NOVARTIS

Clinical Development

LEE011

Clinical Trial Protocol CLEE011X2102 / NCT01747876

A phase I, multi-center, open-label study of LEE011 in patients with malignant rhabdoid tumors and neuroblastoma

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List of abbreviations

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Accumulation ratio
AST	Aspartate aminotransferase
AT	Atypical teratoid
BBB	Blood brain barrier
BLRM	Bayesian Logistic Regression Model
BMA	Bone marrow aspirate
BSA	Body surface area
BSEP	Bile Salt Export Pump
C1D1	Cycle 1, Day 1
CBC	Complete blood count
CCND1	Cyclin D1
CM	Centimeter
C_{max}	Maximum concentration
CNS	Central nervous system
CR	Complete Response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CSF	Cerebrospinal fluid
CRO	Contract Research Organization
CSR	Clinical study report
CV	Coefficient of Variation
DDS	Dose determining set
DLT	Dose Limiting Toxicity
DS&E	Drug Safety and Epidemiology
DOR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EIAED	Enzyme-inducing antiepileptic drug
EOT	End of Treatment
EWOC	Escalation with overdose control
FAS	Full analysis set
FMO3	Flavin-containing monooxygenase 3
FDA	Food and Drug administration
Gd	Gadolinium
Gd-MRI	gadolinium chelate-enhanced brain tumor magnetic resonance imaging
GI	Gastrointestinal
h	Hours
HR	Heart rate
IC_{50}	50% inhibition
ICF	Informed consent form

[redacted]

IEC	Independent ethics committee
IB	Investigator's Brochure
IN	Investigator notification
INRC	International neuroblastoma response criteria
INRG	International neuroblastoma risk group
IRB	Institutional review board
KG	Kilogram
LC/MS/MS	Liquid chromatography-tandem mass spectrometry assay
LLOQ	Lower limit of quantification
LVEF	Left ventricular ejection fraction
MedDRA	Medical dictionary for regulatory activities
mIBG	Metaiodobenzylguanidine
MRT	Malignant rhabdoid tumor
MTD	Maximum Tolerated Dose
MXR	Mitoxantrone-resistant protein
NCI CTCAE	National cancer institute common terminology criteria for adverse events
ORR	Overall response rate
PAS	Pharmacokinetic analysis set
PD	Pharmacodynamics
PE	Physical examination
Pgp	P-glycoprotein
PHI	Protected health Information
PK	Pharmacokinetic
[redacted]	[redacted]
PIB	Powder in Bottle
QTc	QTc Corrected Q-T interval
QTcB	QTcF Corrected Q-T interval (Bazett)
QTcF	QTcF Corrected Q-T interval (Fredericia)
Rb	Retinoblastoma protein
PRBC	Packed red blood cell
PVC	Premature ventricular contractions
RANO	Revised Assessment in Neuro-Oncology
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
RDE	Recommended dose for expansion
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
RT	Rhabdoid Tumor
RTK	Rhabdoid Tumor of the Kidney
SAE	Serious Adverse Event
SD	Standard deviation
SEC	Study Evaluation Completion
SGOT	Serum glutamic oxaloacetic aminotransferase
SGPT	Serum glutamic pyruvic aminotransferase
[redacted]	[redacted]
SUSAR	Suspected unexpected serious adverse event
T1/2	Terminal half-life
TDI	Time-dependent inhibition

[redacted]

TTP	Time to progression
ULN	Upper limit of normal
WBC	White blood cell

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Patient Number	A unique identifier number (consisting of the center number and a patient-specific number) assigned to each patient who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study drug	Any drug administered to the patient as part of the required study procedures; includes investigational drug
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

[redacted]

Amendment 2

Amendment rationale

The primary purpose of this amendment is to add language that describes the option for patients to discontinue treatment in CLEE011X2102 and transfer to a Novartis LEE011 rollover protocol which will continue to provide LEE011.

In addition, for consistency across clinical trials within the LEE011 programs, language has also been updated within the following sections:

- Definition of highly effective contraception method
- Permitted concomitant therapy
- Dosing administration

Changes to Protocol

Sections 4.3, 6.1.3, and 7.1.3 have been updated to include language regarding transfer to the LEE011 rollover protocol.

Section 5.3 Exclusion criterion bullet 16 definition of highly effective contraception method has been updated to align with new internal guidelines.

Section 6.1.2 LEE011 administration was updated to allow administration with food and to include additional citrus fruit to avoid to align with new internal program language.

Section 6.4.1.1 Corticosteroid section was added to include restrictions for corticosteroid use to align with new internal program language.Tables 7-4 and 7-5 sample numbers and PK collection numbers were removed to align with internal guidelines.

IRB/IEC/REB Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, the changes herein affect the Informed Consent and sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

[redacted]

Summary of previous amendment(s)

Amendment 1

18 July 2013

The primary purpose of this amendment was to add additional timepoints to the ECG monitoring to better evaluate and characterize the cardiac repolarization effects of LEE011. In addition, the eligibility criterion was modified to allow the enrollment of patients with tumors other than malignant rhabdoid tumor (MRT) and neuroblastoma who have documented aberrations in the D-cyclin-CDK4/6-INK4a-Rb pathway to the dose escalation part of the study. Information on alternate formulations was added and language around continuous dosing regimen was removed. In addition, updates to some sections, and minor revisions and corrections were made to improve the consistency and clarity of the protocol.

Amendment 1

Amendment rationale

The primary purpose of this amendment is to add additional timepoints to the ECG monitoring to better evaluate and characterize the cardiac repolarization effects of LEE011. In addition, the eligibility criterion is modified to allow the enrollment of patients with tumors other than malignant rhabdoid tumor (MRT) and neuroblastoma who have documented aberrations in the D-cyclin-CDK4/6-INK4a-Rb pathway to the dose escalation part of the study. Information on alternate formulations has been added and language around continuous dosing regimen has been removed. In addition, updates to some sections, and minor revisions and corrections have been made to improve the consistency and clarity of the protocol.

Emerging safety data from the adult phase 1 study (CLEE011X2101) suggests LEE011 has an effect on the cardiac repolarization. Asymptomatic grade 1 or 2 QTcF prolongation has been observed with increasing frequency starting at 600 mg up to 1200 mg. One patient had an asymptomatic grade 3 QTcF prolongation as a dose limiting toxicity at 900 mg, the declared maximum tolerated dose (MTD) in adults. The CLEE011X2101 study is currently exploring intermediate doses to determine the appropriate recommended dose for expansion (RDE) based on safety, PK, and PD data. The RDE in adults will most likely be 600 mg with the 3 week on 1 week off regimen. The starting dose in this study, CLEE011X2102, assumed an adult MTD of 600 mg and remains appropriate. Due to the QTcF changes observed in the adult study, additional time points are being added with triplicate measurements to obtain a more robust evaluation of the ECG changes in pediatric patients.

Besides MRT and neuroblastoma, the D-cyclin-CDK4/6-INK4a-Rb pathway is disrupted in many pediatric tumors including osteosarcoma, rhabdomyosarcoma, Ewing's sarcoma, medulloblastoma, and high grade gliomas. Gene profiling technologies are increasingly identifying pediatric patients with tumors that have these pathway abnormalities and are hence likely to derive benefit from therapy with LEE011. Therefore, patients who have documented evidence of D-cyclin-CDK4/6-INK4a-Rb pathway abnormalities (e.g. cyclin D amplification, CDK4 amplification, p16 loss etc.) will be allowed to enroll in the dose escalation part of the study.

[redacted]

LEE011 will soon be available in a Powder in Bottle (PIB) form for dissolution in water or Ora-Sweet (or equivalent) and a liquid formulation is also under development. This amendment adds language for the use of these alternate dosing formulations when available.

Evaluation of the continuous dosing regimen was performed in the adult phase 1 study (CLEE011X2101). This regimen was not well tolerated and will not be pursued any longer. Therefore all references to this alternate dosing regimen will be removed from this protocol.

Changes to Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions

- Section 1.2.1.2 Clinical experience has been updated with CLEE011X2101 clinical experience.
- Table 3-1 Objectives and endpoints has been updated to include PK parameters as a secondary endpoint
- Section 5.2 Inclusion Criterion #2 revised to include “in dose escalation part, other tumors with documented evidence of D-cyclin-CDK4/6-INK4a-Rb pathway abnormalities”
- Sections 6.1 Study Treatment and 6.6 Study drug dispensation revised to include Powder in Bottle and liquid formulations.
- Section 6.1.1 Alternate dosing regimen of LEE011 revised to remove daily continuous dosing regimen (28 day cycle).
- Section 6.1.2 LEE011 administration text has been revised to standardize with other LEE011 protocols and now reads “Any doses that are missed (not taken within 6 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day.”
- Sections 6.1.2 LEE011 administration and 7.2.3.1 PK blood sample collection and handling has been revised to include additional PK timepoints due to administration or formulation switch.
- Section 6.2.2 Guidelines for dose escalation and determination of (MTD/ RDE) has been revised to standardize with Novartis standard language.
- Section 7.2.1 Efficacy assessments has been revised to include “All radiological assessments obtained for all patients enrolled during the study will be centrally collected and subjected to quality checks by an imaging CRO selected by Novartis. The site manual provided by the designated imaging CRO will provide further details regarding image collection.”
- Section 7.2.2.5.5 Electrocardiogram has been revised to include additional ECG timepoints (C1D8 and C1D15) and for all timepoints to be performed in triplicate.
- Section 10.5.2.4 Electrocardiogram has been added to describe ECG analyses.
- Section 10.6.2 PK-QTc relationship has been added to describe PK-QTc relationship analyses.

[redacted]

IRB/IEC/REB Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, the changes herein affect the Informed Consent and sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

[redacted]

Protocol summary

Protocol number	LEE011X2102
Title	A phase I, multi-center, open-label study of LEE011 in patients with malignant rhabdoid tumors and neuroblastoma
Brief title	Study of safety and efficacy in patients with malignant rhabdoid tumors (MRT) and neuroblastoma
Sponsor and Clinical Phase	Novartis; Phase I
Investigation type	Drug
Study type	Interventional
Purpose and rationale	LEE011 is a small molecule inhibitor of CDK4/6. In the Novartis Cell Line Encyclopedia screen, malignant rhabdoid tumor (MRT) and neuroblastoma cell lines were among the most sensitive to LEE011. LEE011 has demonstrated *in vitro* and *in vivo* activity in both tumor models. The primary purpose of this study is to determine the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) in pediatric patients and to delineate a clinical dose to be used in future studies. This study will also assess the safety, tolerability, PK and preliminary evidence of antitumor activity of LEE011 in patients with MRT, neuroblastoma or other tumors with D-cyclin-CDK4/6-INK4a-Rb pathway abnormalities.
Primary Objective	Estimate the MTD and/or RDE of LEE011 as a single agent when administered orally to patients
Secondary Objectives	Objective 1: Characterize the safety and tolerability of LEE011 Objective 2: Characterize pharmacokinetics of LEE011 and any clinically significant metabolites that may be identified Objective 3: Assess the anti-tumor activity of LEE011
Study design	This is a two-part, phase 1 study, with a dose escalation part followed by an expansion part. The expansion part will start after the MTD/RDE has been determined. The expansion part will include 2 groups of patients, one restricted to MRT patients with either CNS or extra-CNS primary and the second including neuroblastoma patients. LEE011 will be administered orally, once daily for 21 days followed by a 1 week break (28-day cycle).
Population	Patients, aged 12 months to 21 years, with MRT or neuroblastoma
Inclusion criteria	● Confirmed diagnosis of MRT, neuroblastoma, or in the dose escalation part, other tumors with D-cyclin-CDK4/6-INK4a-Rb pathway abnormalities, that has progressed despite standard therapy or for which no effective standard therapy exists. ● Age ≥ 12 months and ≤ 21 years ● Patients with CNS disease should be on stable doses of steroids for at least 7 days prior to first dose of LEE011 with no plans for escalation. ● In expansion part, patients must have at least one measurable disease as defined by RECIST v1.1. ● Patients must have a Lansky (≤ 16 years) or Karnofsky (> 16 years) score of at least 50. ● Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to enrollment.

[redacted]

Exclusion criteria	● Prior history of QTc prolongation or QTcF > 450 ms on screening ECG. ● Patients with the following laboratory values during screening: ● Serum creatinine > 1.5 x upper limit of normal (ULN) for age ● Total bilirubin >1.5 x ULN for age ● Alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT) > 3 x ULN for age; aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase/SGOT > 3 x ULN for age except in patients with tumor involvement of the liver who must have AST/SGOT and ALT/SGPT ≤ 5 x ULN for age. For the purpose of this study, the ULN for SGPT/ALT is 45 U/L. ● Patients who are currently receiving treatment with agents that are metabolized predominantly through CYP3A4/5 and have a narrow therapeutic window and/or agents that are known strong inducers or inhibitors CYP3A4/5 are prohibited. In particular, enzyme-inducing antiepileptic drugs (EIAEDs). ● Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may interfere with the interpretation of study results, and in the judgment of the investigator would make the patient inappropriate for the study.
Investigational and reference therapy	LEE011
Efficacy assessments	● Overall response rate (ORR), duration of response (DOR) and time to progression (TTP) as per RECIST 1.1 in patients. In addition, response by INRC for neuroblastoma patients and response by RANO Criteria for primary CNS tumors patients.
Safety assessments	● Incidence rate of Dose Limiting Toxicities (DLT) during the first cycle of LEE011 treatment ● Adverse events and serious adverse events, changes in laboratory values, assessments of physical examinations, vital signs and electrocardiograms
Other assessments	● Plasma concentration time profiles, PK parameters, including but not limited to AUCtau, Cmax, Tmax, CL/F, accumulation ratio (Racc), and T1/2,acc ● [redacted]
Data analysis	The primary purpose of the study is to estimate the MTD and/or the RDE of LEE011 when administered as a single agent orally in patients The corresponding primary endpoint is the incidence of DLTs in cycle 1. Estimation of the MTD of the treatment will be based upon the estimation of the probability of DLT in Cycle 1 for patients in the DDS (see definition below), using an adaptive BLRM guided by the EWOC principle. Unless otherwise specified, the Full Analysis Set (FAS) will be the default analysis set used for all analyses. It includes all patients who received at least one dose of LEE011. For all safety analyses, the safety set will be used. It includes all patients who received at least one dose of LEE011, and have at least one valid post-baseline safety assessment. The dose-determining set (DDS) will be used for the estimation of MTD. It consists of all patients from the safety set who meet a minimum exposure criterion as outlined in Section 10 and have sufficient safety evaluations, or discontinue earlier due to DLT. Anti-tumor activity will be summarized in terms of overall response rate (ORR), duration of response (DOR), and time to progression (TTP) All biomarker data will be listed and summarized using frequency tables. In particular, [redacted] The study data will be analyzed and reported based on all patients' data of the dose escalation and expansion parts. Details of the statistical analysis and data reporting will be provided in the Novartis Report and Analysis Plan (RAP) document finalized prior to database lock.
Key words	Phase I, pediatric, open-label, dose escalation, malignant rhabdoid tumors, MRT, neuroblastoma

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Malignant Rhabdoid Tumors

Malignant Rhabdoid Tumors are extremely aggressive malignancies that generally occur in infants and young children. The most common locations are in the kidney and central nervous system (CNS), although they can arise in most soft-tissue sites. Rhabdoid tumors in all anatomical locations have a similar molecular origin (Biegel 2006). The incidence rate of MRT is about 1 per million children per year (Woehrer et al 2010). These tumors have no standard or effective therapeutic regimens. Most patients receive intensive multimodality treatment including surgery, radiotherapy, chemotherapy, and sometimes high-dose chemotherapy with stem-cell rescue. Despite this aggressive approach, prognosis for children with MRT is poor. Mean survival with surgical intervention alone is 3 months and with adjuvant chemotherapy and radiotherapy is 8 months (Tekautz et al 2005). Therefore, the development of new strategies with less toxicity burden and with more targeted drugs is warranted.

Near-uniform biallelic inactivating mutations in [redacted] a gene that encodes a core subunit of the SWI/SNF chromatin remodeling complex, are seen in more than 95% of MRTs (Versteege et al 1998). Studies have revealed that MRTs are exquisitely dependent on cyclin D1 (CCND1) for genesis and survival, and loss of INI1leads to de-repression of cyclin D1 in primary mouse and human MRTs (Tsikitis 2005, Fujisawa 2005, McKenna 2008). Genetic abrogation of CCND1 eliminates MRT formation in Ini1+/− mice, and siRNA-mediated knockdown of CCND1 is sufficient to induce G0/G1 arrest and apoptosis in MRT cells (Tsikitis et al 2005). These studies, suggest that targeting Cyclin D1 or the Cyclin/CDK axis could be an effective means of inhibiting MRT growth.

Neuroblastoma

Neuroblastoma is the most common extracranial solid cancer in childhood and the most common cancer in infancy, with an annual incidence of about 650 cases per year in the US. The median age at diagnosis is 17 months (London et al 2005). The tumors arise in tissues of the sympathetic nervous system, typically in the adrenal medulla or paraspinal ganglia. These tumors are biologically heterogeneous with a broad spectrum of clinical behavior. Approximately 50% of patients present with metastatic disease. Genetic alterations in ALK have been reported in approximately 15% (Mosse et al 2008) and MYCN amplifications in about 25% of tumors (Brodeur et al 1984). Patients with segmental chromosomal aberrations display wide phenotypic variability and have poor prognosis. Outcomes in patients with standard risk neuroblastoma have improved over the past decades (Cohn et al 2009). However, despite intensive therapy, the survival rates among children with high-risk neuroblastoma have shown only modest improvement; 50 to 60% of the patients relapse and no salvage treatment regimens are known to be curative (Maris 2010). Novel approaches to treating these patients are required to improve their outcome.

[redacted]

The Rb signaling pathway is important for neuronal differentiation and migration (McClellan and Slack 2006). High incidence of Cyclin D1 and CDK4 over-expression has been observed in neuroblastoma cell lines (Molenaar et al 2008). Copy number defects of G1-cell cycle genes (CCND1, CDK4 and CDK6) occur in 30% of patients and correlate with high expression of E2F target genes and a poor prognosis (Molenaar et al 2012). Therefore, targeting the CCND1/CDK4 axis may provide therapeutic benefit to high-risk neuroblastoma patients.

1.2 Introduction to investigational treatment

1.2.1 Overview of LEE011

LEE011 is an orally bioavailable, small molecule inhibitor of CDK4/6. LEE011 exhibits highly specific inhibitory activity against CDK4/cyclinD1 and CDK6/cyclinD3 complexes, with concentration resulting in 50% inhibition (IC_{50}) values of 10 nM and 39 nM, respectively, in isolated enzyme assays. It is inactive against the majority of other kinases. It is currently being tested in a clinical trial in adult cancer patients [CLEE011X2101].

1.2.1.1 Non-clinical experience

1.2.1.1.1 Pharmacology

LEE011 inhibits the growth of many tumor cell types *in vitro* and *in vivo*, including mantle cell lymphoma, liposarcoma, melanoma, and carcinomas of the esophagus, breast, lung and pancreas. Regardless of the various genetic aberrations that may be present in the cancer cells, the anti-tumor activity of LEE011 requires the presence of functional retinoblastoma protein (Rb).

In the Novartis Cell Line Encyclopedia screen, MRT and neuroblastoma cell lines were among the most sensitive to LEE011. In *in vitro* pharmacology studies, LEE011 induces anti-proliferative effects in MRT (A204, G401) and neuroblastoma cell lines (SK-N-DZ, CHP212, IMR-32, KP-N-YN, KELLY, SK-N-BE(2)).

In *in vivo* pharmacology studies, LEE011 demonstrated tumor growth suppression in MRT and neuroblastoma xenograft models. ALK mutation & MYCN status in neuroblastoma cells do not appear to be associated with LEE011 sensitivity. The majority (90-100%) of MRT and neuroblastoma tumors have functional Rb.

1.2.1.1.2 Nonclinical PKs and metabolism

The PK of LEE011 was investigated in four different species: mouse, rat, dog and monkey.

After oral administration to rats, LEE011 was moderately absorbed (48 to 84%) with bioavailability ranging from 10% and 65% across animal species. Maximum serum drug concentration (Cmax) was between 2 and 4 hours (h). The terminal half-life (T1/2) of LEE011 was moderate in rodents and monkeys (2 to 7 h), and was comparatively longer (18 h) in dogs. The predicted human PK parameters based on allometric scaling were 1259 mL.min-1 (75.5 L.h-1) for CL/F, 2334 L for Vss/F, with a T1/2 of around 21 hours.

[redacted]

The binding of LEE011 to plasma proteins was moderate (unbound fraction in plasma for humans is 30 ± 2%). ^{3}H-LEE011 and its metabolites are extensively distributed into the organs and tissues of rats including choroid, ciliary body and meninges with the exception of the brain. The highest radioactivity concentrations were found in tissues such as pituitary gland, pineal gland, spleen, kidney and adrenal medulla with remarkably high exposure in the thyroid gland. Distribution of LEE011 and/or its metabolites into melanin-containing structures was seen in pigmented rats.

Oxidative metabolism of LEE011 is dominated by CYP3A4 with a minor contribution of about 20% by flavin-containing monooxygenase 3 (FMO3). LEE011 is a moderate substrate of P-glycoprotein (Pgp). LEE011 is a time-dependent CYP3A4 inhibitor and a reversible inhibitor of CYP1A2. LEE011 was found to inhibit the mitoxantrone-resistant protein (MXR), and human bile salt export pump (BSEP) but not rat or dog BSEP. LEQ803 (N-demethylation) is a major metabolite in the rat and monkey, the main metabolite in humans and the only metabolite in dogs. This metabolite was found to interact with hERG channels *in vitro*.

In rat ADME studies, LEE011 was predominantly excreted with bile. The elimination of unchanged drug was limited. A minor proportion of the administered dose is excreted in urine. The bulk of the administered dose (87.3%) was excreted within 24 hours.

Overall, the elimination of LEE011 may potentially be affected by co-administered drugs that inhibit or induce CYP3A4. LEE011 may inhibit CYP3A4, CYP1A2 and BSEP depending on the dose administered.

Please refer to LEE011 Investigator Brochure (IB) for additional details.

1.2.1.1.3 Safety pharmacology and toxicology

In vitro, LEE011 did not show mutagenic or phototoxic potential.

Safety pharmacology studies did not reveal any effects on CNS or respiratory functions. In the dog telemetry study, prolongation of the average QT and QTc was observed with the potential to induce premature ventricular contractions (PVCs) at higher exposure levels. LEE011 and LEQ803 likely contributed to the QT prolonging effects seen *in vivo*.

In rats and dogs, LEE011 induced bone marrow hypocellularity, lymphoid depletion, atrophy of the skin and intestinal mucosa, decreased bone formation and testicular atrophy. These are consistent with the mechanism of action of LEE011. In addition, an increased number of ovarian corpora lutea was observed in a single female dog at the highest dose tested. The liver, bile system and gall bladder (proliferative changes, cholestasis, sand-like gallbladder calculi, and inspissated bile) were identified as additional target organs of toxicity which are not likely related to the primary pharmacology of LEE011. Correlating hematological and/or biochemistry changes were seen for the effects described in the bone marrow, lymphoid system and liver. All the described changes were fully reversible in rats and dogs.

Based on its mechanism of action and preclinical toxicology studies, the major potential toxicities for LEE011 include myelosuppression, hepatic toxicity, and prolongation of the QT interval. The risk of these toxicities may be amplified by concomitant administration of strong inhibitors of CYP3A4.

[redacted]

Please refer to LEE011 Investigator Brochure (IB) for additional details.

1.2.1.2 Clinical experience

As of 4 February 2013, 56 patients have been treated with single agent LEE011 in the first-in-human phase I study [CLEE011X2101] in which LEE011 is administered orally, once daily for 21 days followed by a 1 week rest (28-day cycle). Doses tested include 50 mg (n=4), 70 mg (n=2), 140 mg (n=4), 260 mg (n=4), 280 mg (n=4), 350 mg (n=5), 400 mg (n=5), 600 mg (n=4), 900 mg (n=13), 750 mg (n=8), and 1200 mg (n=3). In all, 8 DLTs have been observed. DLTs include grade 3 mucositis (n=1) in the 50 mg cohort, grade 3 pulmonary embolism (n=1) in the 280 mg cohort, grade 3 hyponatremia (n=1) and prolonged grade 3/4 neutropenia (n=1) in the 400 mg cohort, grade 4 thrombocytopenia (n=1) in the 750 mg cohort, grade 3 asymptomatic QTc prolongation with grade 3 neutropenia (n=1) in the 900 mg cohort and grade 4 febrile neutropenia (n=1) and grade 4 thrombocytopenia (n=1) in the 1200 mg cohort. The grade 3 mucositis observed in the 50 mg cohort was later determined to be due to herpes simplex virus (HSV) infection. A DLT related to mucositis has not been observed since. Four cases of Grade 1 or 2 mucositis have been observed in doses up to 350 mg; mucositis has not been observed at higher doses. The grade 3 pulmonary embolism was observed in a patient with NSCLC who had diffuse bilateral lung disease and a central venous catheter. The grade 3 hyponatremia was asymptomatic and readily corrected with saline infusion.

Grade 3 or 4 neutropenia and/or thrombocytopenia not meeting DLT criteria were seen in increasing frequency starting from 600 mg up to 1200 mg. Asymptomatic grade 1 or 2 QTc prolongation were observed in increasing frequency starting at 600 mg up to 1200 mg; 1 patient (25%) in the 600 mg cohort, 2 patients (25%) in the 750 mg cohort, 4 patients (31%) in the 900 mg cohort, and 3 patients (100%) in the 1200 mg cohort. The most frequently reported treatment-related AEs include fatigue, nausea, anemia, asthenia, neutropenia, vomiting, leukopenia, increased blood creatinine, decreased appetite, diarrhea, hypoalbuminemia, lymphocytopenia, myalgia, thrombocytopenia, dizziness, erythema, hyperglycemia, mucosal inflammation and stomatitis. The majority have been grades 1 or 2 and reversible.

The MTD of LEE011 for the 3 weeks on/1 week off schedule was determined to be 900 mg. Continuous dosing with LEE011 at 600 mg was also evaluated. This dosing regimen was not well tolerated and will therefore not be pursued further. The study continues to explore intermediate doses to establish the RDE and further assess the safety, tolerability, and preliminary anti-tumor activity of LEE011.

1.2.1.3 Clinical pharmacokinetics

Preliminary PK data up to the 1200 mg dose cohort in phase I study [CLEE011X2101] haveshown slightly over-proportional increases in exposure across the dose range tested. Steady-state is reached by day 8. Accumulation ratio (Racc) calculated from AUCtau on day 21 and AUCtau after a single dose on day 1 across the studied doses of 50 to 600 mg ranged from 1.55- to 2.94-fold. Effective T1/2 (T1/2,eff) based on drug accumulation ranges from 24 hours (50 mg QD dose) to 40 hours (600 mg QD dose).

[redacted]

2 Rationale

2.1 Study rationale and purpose

As described in Section 1, targeting the D-Cyclin/CDK axis may be an effective means of inhibiting growth of MRT and neuroblastoma. Evaluation of LEE011 in pediatric patients at this early stage in development is driven by the strong biological rationale, supporting preclinical data, and the urgent need for effective targeted therapies in these 2 indications. It has been well established that children have similar or higher threshold for toxicity when compared to adults despite multiple intensive prior therapies (Lee 2005; Kim 2008; EMA 2003). Safety and PK data from pediatric patients will be used to guide dose-escalation and refine dosing in this study.

Enrollment includes patients with neuroblastoma or MRT because LEE011 has shown most in vitro and in vivo activity in these 2 indications. Evidence of anti-tumor activity in these 2 indications will be used to inform future development of LEE011 in these and other pediatric tumors where this pathway may be critical for tumorigenesis. Preclinical studies showed more than 95% of MRT and neuroblastoma have an intact pRb. Therefore, pre-screening for pRb status will not be required.

The D-cyclin-CDK4/6-INK4a-Rb pathway is also disrupted in many other pediatric tumors including osteosarcoma, rhabdomyosarcoma, Ewing's sarcoma, medulloblastoma, and high grade gliomas. Gene profiling technologies are increasingly identifying pediatric patients with tumors that have these pathway abnormalities and have the potential to derive benefit from therapy with LEE011. Therefore, patients who have documented evidence of D-cyclin-CDK4/6-INK4a-Rb pathway abnormalities (e.g. cyclin D amplification, CDK4 amplification, p16 loss etc.) will be allowed to enroll in the dose escalation part of the study.

Although in preclinical studies, LEE011 does not cross the blood brain barrier (BBB), exploration of its activity in MRT and other brain tumors is considered worthwhile due to the tumors' dependency on the cyclinD/CDK pathway and the potential for LEE011 to benefit these patients who have no effective therapy. Evaluation of LEE011 in patients with primary CNS MRT is supported by evidence that the BBB in most CNS tumors is disrupted. Systemic chemotherapy has been effective in many cases (Deeken and Loscher 2007). Moreover, surgery and radiation therapy performed as initial treatment in these patients increase the likelihood that this barrier will be disrupted. The superior outcomes of doxorubicin-based regimens in MRT, a drug that does not cross the BBB, attest to this fact (Chi et al 2009).

The primary purpose of this study is to determine the MTD and/or RDE in pediatric patients, and to delineate a clinical dose to be used in future studies. This study will also assess the safety, tolerability, PK and preliminary evidence of antitumor activity of LEE011 in patients with MRT, neuroblastoma or other tumors with D-cyclin-CDK4/6-INK4a-Rb pathway abnormalities.

2.2 Rationale for the study design

This is a multi-center, open-label phase 1 study limited to patients aged 12 months to 21 years old who have MRT or neuroblastoma. Patients with both primary CNS and extra-CNS MRT will be eligible. In addition, patients who have documented evidence of D-cyclin-CDK4/6-

[redacted]

INK4a-Rb pathway abnormalities will be allowed to enroll in the dose escalation part of the study. Patients must have disease that has progressed following standard therapy or for which no standard treatment option exists. The study includes an expansion at the MTD and/or RDE in order to better evaluate safety, tolerability, and preliminary evidence of antitumor activity in MRT and neuroblastoma.

There will be no pre-screening for Rb in the study due to the high frequency of intact Rb in these tumor types. Rb gene status and presence of Rb protein in tumors will be determined retrospectively in those patients who enroll in the study.

This study will utilize a BLRM which is a well-established method to estimate the MTD and/or RDE in cancer patients. The adaptive BLRM will be guided by the EWOC principle to control the risk of DLT in future patients on study. This method is more likely to assign fewer patients to either sub-therapeutic or severely toxic dose levels and estimate the MTD with smaller average bias and error than the up-and-down methods such as 3+3. The use of Bayesian response adaptive models for small datasets has been accepted by EMA ("Guideline on clinical trials in small populations" February 1, 2007) and endorsed by numerous publications (Babb 1998; Neuenschwander 2008; Neuenschwander 2010), and its development and appropriate use is one aspect of the FDA's Critical Path Initiative.

2.3 Rationale for dose and regimen selection

The MTD of LEE011 for the 3 weeks on/1 week off schedule is 900 mg. The RDE in adults will most likely be 600 mg on the same regimen. The dose from the adult Phase 1 study that will be used to calculate the starting dose in children is 600 mg/d. This is based upon review of the safety, tolerability, and PK observed at this dose level and higher. At the 600 mg/d dose in adults, LEE011 was well tolerated with an acceptable safety profile. At this dose, systemic exposures corresponding to efficacy in preclinical models was observed. On target toxicity, neutropenia, was seen but not dose-limiting. Therefore, using the 600 mg/d dose from the adult study for calculating the starting dose in children offers a high probability of beginning at an active dose and a low probability of excessive toxicity.

The first cohort of children in this trial will be treated with a dose of 280 mg/m^2/d, which is 80% of the current well tolerated dose (600 mg/d) in the ongoing adult study [CLEE011X2101] divided by the average adult body surface area (BSA) of 1.72 m^2. Refer to Section 6.2.1 for details.

In adults, LEE011 is dosed once daily orally, and the T1/2, acc ranges from 24.2 to 40 hours. This supports once daily dosing in children. LEE011 will be dosed once a day for 21 consecutive days followed by a 7-day planned break as part of each 28-day cycle of treatment consistent with the regimen used in [CLEE011X2101].

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4.
Determine the MTD and/or RDE of LEE011	Incidence rate of DLTs in Cycle 1	
Secondary		Refer to Section 10.5.
(1) Characterize the safety and tolerability of LEE011	(1) AEs and serious adverse events (SAEs), changes in laboratory values and electrocardiograms (ECGs).	
(2) Characterize the PK of LEE011 and any clinically significant metabolites that may be identified	(2) Plasma concentration time profiles of LEE011, PK parameters, including but not limited to AUCtau, Cmax, Tmax, CL/F, accumulation ratio (Racc), and T1/2,acc	
(3) Assess the anti-tumor activity of LEE011	(3) Overall response rate (ORR), duration of response (DOR), and time to progression (TTP) per RECIST 1.1. In addition, for neuroblastoma, response by INRC. In addition, for primary CNS tumors, response by RANO Criteria.	
Exploratory		Refer to Section 10.6.
(1) [redacted]	(1) [redacted]	
(2) Evaluate PD effects in patients with neuroblastoma	(2) Changes in biomarkers associated with the pharmacologic activity of LEE011 ([redacted] by comparing pre-treatment and post-treatment samples when available.	
(3) To characterize the relationship between QTc prolongation and exposure to LEE011 and/or any of its relevant metabolites.	(3) ECG interval parameters (e.g. QTcF, QTcB, QT, QRS, RR, PR, HR), plasma concentration time profiles of LEE011and PK parameters such as Cmin, Cmax, AUCtau	

[redacted]

4 Study design

4.1 Description of study design

This is a phase 1, multi-center, open-label study, with a dose escalation part followed by an expansion part. Eligible patients aged 12 months to 21 years old whose tumor has progressed following standard therapy, or for which no standard, effective therapy exists will be enrolled in the study. LEE011 will be administered orally, once daily for 21 days followed by a 1 week break (28-day cycle) at the starting dose of 280 mg/m^2/d.. For the purpose of scheduling assessments and establishing the MTD/RDE, a cycle is defined as 28 days in length.

During the dose escalation part, 3-6 newly enrolled patients in successive cohorts will receive increasing doses of LEE011 with the dosing schedule specified above. A BLRM using the EWOC principle will be used to guide dose escalation. During the course of dose escalation, additional patients may be enrolled to previously tested lower dose levels that have been assessed as safe and well-tolerated if there is no slot available in the current cohort under testing. It is expected that approximately 10 patients may be enrolled and treated within this context. In all, it is anticipated that approximately 28 patients will be treated during the escalation part.

Once the MTD/RDE has been determined, the expansion part will begin to better characterize the safety, tolerability and PK profile of LEE011, as well as assess preliminary antitumor activity of LEE011. During the expansion part of the study LEE011 will be dosed at the MTD, or at a lower RDE, if the available data suggest that the MTD is not appropriate for multiple cycles of therapy. This part will include 2 arms, one restricted to neuroblastoma patients and the second to MRT patients with either CNS or extra-CNS primary. A minimum of 8 patients each will be required for CNS and extra-CNS primary MRT. Enrollment will proceed in parallel. Patients enrolled during the expansion part of the study are required to have measurable disease. Approximately 18 patients will be treated in each arm, for a total of approximately 36 patients in the expansion part.

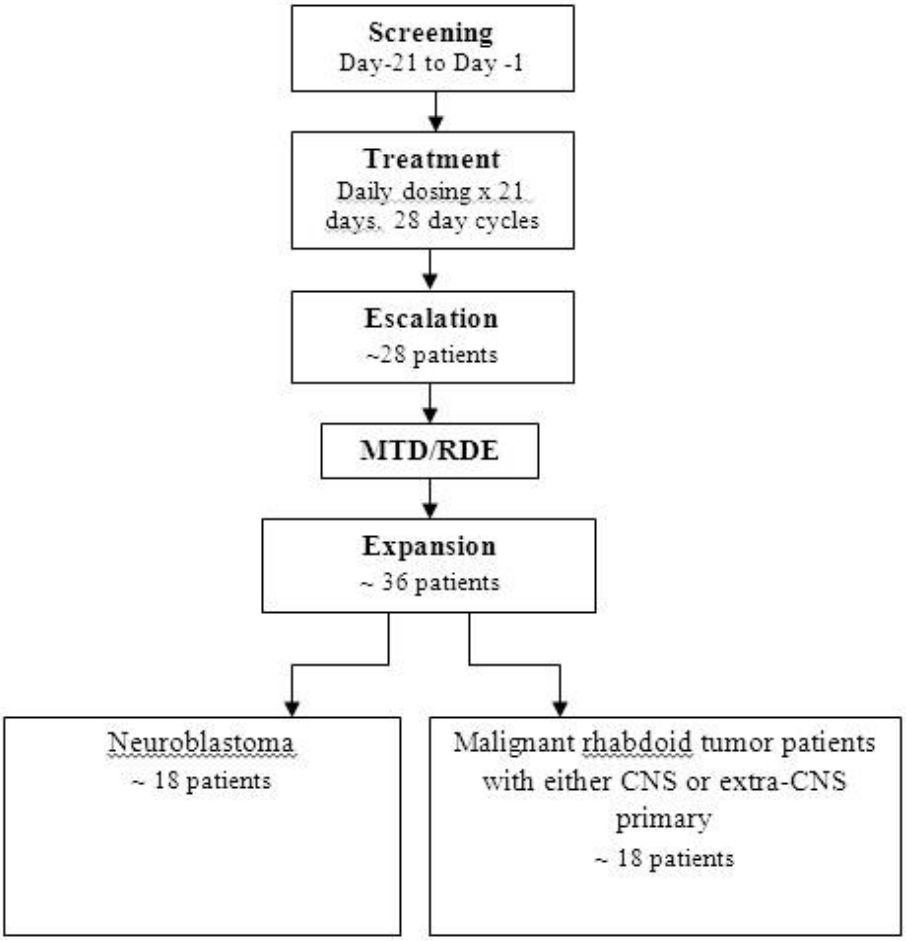
All patients will be required to provide archival tumor biopsies (at diagnosis or relapse) unless otherwise agreed upon by Novartis and the investigator. At screening, all patients with neuroblastoma will undergo bilateral bone marrow aspirates (BMA) and/or biopsy and will be examined for presence of disease per standard institutional practice. Patients with bone marrow involvement at study entry will have repeat bone marrow evaluations for disease response at periodic intervals during the study. If feasible, pre- and post-treatment bone marrow samples (BMA and/or biopsy) will be collected from these patients. All patients with primary CNS tumors (including MRT) will be required to have a cerebrospinal fluid (CSF) sample drawn at screening and examined for presence of tumor cells unless otherwise agreed upon by Novartis and the investigator. Patients with CSF positive for disease at screening will require a repeat CSF examination for confirmation of Complete Response (CR). If CSF is collected as part of efficacy assessment or if CSF is collected as part of routine/standard care at any time after patient has received first dose of LEE011, a sample will be requested for testing LEE011 levels in the CSF. If feasible, a PK blood sample corresponding to the timing of CSF collection will also be requested.

[redacted]

Patients will continue to receive treatment with LEE011 until disease progression, occurrence of unacceptable toxicity that precludes any further treatment, or if treatment is discontinued at the discretion of the investigator or by patient's withdrawal of consent. All patients will have an EOT visit within 14 days of permanently discontinuing LEE011 and will be followed for 30 days after last dose of study treatment. Analysis of the study data may occur after all patients have had the opportunity to complete at least 6 cycles of treatment.

Approximately 64 patients will be treated in the entire study.

Figure 4-1 Overview of study design



4.2 Timing of interim analyses and design adaptations

No formal interim analyses are planned.

4.3 Definition of end of the study

The study data will be analyzed and reported in the primary Clinical Study Report (CSR) taking into account all patients' data of the dose escalation and expansion parts up to the time when all patients continuing to receive treatment have completed at least six cycles of treatment with LEE011, all patients have discontinued from the study, the study is terminated early, or another clinical study that can continue to provide drug becomes available and all

[redacted]

patients ongoing are transferred to that clinical study, whichever comes first. After the primary CSR analysis, any additional data collected will be included in a supplementary analysis once all patients have discontinued the study. It will be reported in an addendum to the CSR, as appropriate.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be contacted within 24 hours, informed to stop taking the study drug and be seen as soon as possible. The same assessments should be performed as described in Section 7.1.3 and Section 7.1.4 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

No pre-screening for Rb will be required. Testing for Rb will be done retrospectively.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria in order to be offered treatment in the study.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Age ≥ 12 months and ≤ 21 years at time of signing consent form
2. Confirmed diagnosis of MRT, neuroblastoma or in dose escalation part, other tumors with documented evidence of D-cyclin-CDK4/6-INK4a-Rb pathway abnormalities, that has progressed despite standard therapy or for which no effective standard therapy exists.
   a. MRT includes diagnoses of Atypical Teratoid/Rhabdoid Tumor (AT/RT), and Rhabdoid Tumor of the Kidney (RTK) and other soft tissues as defined by 2 of the 3 following criteria: a) Morphology and immunophenotypic panel consistent with rhabdoid tumor b) Loss of [redacted] confirmed by immunohistochemistry c) Molecular confirmation of tumor-specific bi-allelic [redacted] loss/mutation is encouraged in cases where [redacted] immunohistochemistry is equivocal, and required if [redacted] immunohistochemistry is not available. Patients should have either a+b or a+c.
   b. Diagnoses of neuroblastoma must be either by histologic verification of neuroblastoma and/or demonstration of tumor cells in the bone marrow with increased urinary catecholamines.
   c. Patients with other tumor types who have documented evidence of D-cyclin-CDK4/6-INK4a-Rb pathway abnormalities (e.g. cyclin D amplification, CDK4 amplification, p16 loss, etc.) will be allowed to enroll in the dose escalation part of the study.
3. Patients with CNS disease should be on stable doses of steroids for at least 7 days prior to first dose of LEE011 with no plans for escalation.

[redacted]

4. Patients must meet the following hematologic criteria:
   a. Peripheral absolute neutrophil count (ANC) ≥ 1000/µL without growth factor support within 7 days prior to first dose of LEE011
   b. Platelet count ≥ 75,000/µL without platelet transfusions within 7 days prior to first dose of LEE011
   c. Hemoglobin ≥ 8.0 g/dL without blood transfusions within 7 days prior to first dose of LEE011
5. Patients with bone marrow metastatic disease who do not meet the above criteria will be eligible to enroll in the **expansion part** of the study with the following count criteria. These patients will not be evaluable for hematologic toxicity or hematologic DLT.
   a. ANC > 750/µL within 7 days prior to first dose of LEE011
   b. Platelet count > 50,000/µL (may receive platelet transfusions) within 7 days prior to first dose of LEE011
   c. Hemoglobin ≥ 7.5 g/dL (may receive RBC transfusions) within 7 days prior to first dose of LEE011
6. Extent of disease (Refer to Appendix 1, Appendix 2 and Appendix 3).
   - For the **dose escalation part** of the study patients must have evaluable and/or measurable disease.
   - For the **dose expansion part** of the study patients must have at least one measurable disease as defined by RECIST v1.1. Neuroblastoma patients with positive MIBG (metaiodobenzylguanidine) scan will be eligible and considered evaluable and measurable. Neuroblastoma patients with bone marrow-only disease will NOT be eligible. If palliative XRT has been administered, at least one measurable lesion must not have been irradiated. Previously irradiated lesions must demonstrate clear evidence of progression to be considered measurable.
7. All patients should submit an archival tumor biopsy specimen (collected at diagnosis or relapse). Patients who have no tumor tissue available may be permitted to participate after discussion with Novartis and the investigator.
8. Patients must have a Lansky (≤ 16 years) or Karnofsky (> 16 years) score of at least 50. Patients who are unable to walk because of paralysis, but who are sitting up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score. (Refer to Appendix 4, Appendix 5).
9. Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to enrollment.
10. Written informed consent/assent before any study-specific screening procedures. For pediatric patients, consent will be obtained from parent(s) or legal guardian(s) and the signature of at least 1 parent or guardian will be required. Investigators will also obtain assent of patients according to local, regional or national guidelines.

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Malignant disease, other than that being treated in this study.
2. Patients with the following laboratory values during screening:

[redacted]

a. Serum creatinine > 1.5 x upper limit of normal (ULN) for age
b. Total bilirubin >1.5 x ULN for age
c. Alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT) > 3 x ULN for age; aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase/SGOT > 3 x ULN for age except in patients with tumor involvement of the liver who must have AST/SGOT and ALT/SGPT ≤ 5 x ULN for age. For the purpose of this study, the ULN for SGPT/ALT is 45 U/L.

3. Systemic antineoplastic therapy or any experimental therapy within 3 weeks before the first dose of LEE011 (6 weeks if prior nitrosourea or bevacizumab).
4. Radiotherapy within 2 weeks before the first dose of LEE011 (< 6 wks for therapeutic doses of MIBG)
5. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of LEE011 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
6. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may interfere with the interpretation of study results, and in the judgment of the investigator would make the patient inappropriate for the study.
7. Major surgery within 2 weeks of the first dose of LEE011. Gastrostomy, insertion of a gastric feeding tube (G-tube), ventriculo-peritoneal shunt, endoscopic ventriculostomy and central venous access are not considered major surgery.
8. Autologous stem cell transplant following myeloablative therapy within 3 months prior to the first dose of LEE011 or prior allogeneic stem cell transplant at any time. Patients who received stem cell reinfusion following non-myeloablative therapy are eligible once they meet peripheral blood count criteria in Inclusion Criterion #4
9. Uncontrolled cardiovascular condition, including ongoing cardiac arrhythmias, congestive heart failure, angina, or myocardial infarction within 6 months prior to the first dose of LEE011.
10. Prior history of QTc prolongation or QTcF > 450 ms on screening ECG.
11. Left ventricular ejection fraction (LVEF) < 45%
12. Prior exposure to CDK4/6 inhibitor.
13. Patients who are currently receiving treatment with agents that are known to cause QTc prolongation in humans. (Refer to Appendix 6).
14. Patients who are currently receiving treatment with agents that are metabolized predominantly through CYP3A4/5 and have a narrow therapeutic window and/or agents that are known strong inducers or inhibitors CYP3A4/5 are prohibited. In particular, enzyme-inducing antiepileptic drugs (EIAEDs). (Refer to Appendix 6).
15. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test
16. Women of child-bearing potential (Refer to Section 7.2.2.5.4), defined as all women physiologically capable of becoming pregnant (who have attained menarche), **unless** they are using highly effective methods of contraception during dosing of study treatment and for 21 days after stopping study treatment. Highly effective contraception methods include:

[redacted]

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that patient.
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

6 Treatment

6.1 Study treatment

For this study, the term "investigational or study drug" refers to LEE011. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

6.1.1 Dosing regimen

LEE011 is provided to investigational sites in capsule, powder in bottle (PIB) or liquid forms for oral use. LEE011 will be taken orally, once a day for 21 consecutive days followed by a 7-day planned break.

LEE011 dose will be scaled by Body Surface Area (BSA). The dose will be adjusted to the nearest 10 or 50 mg (higher or lower) as appropriate. The investigational site staff will inform each patient of their actual daily dose, and this will be recorded on the appropriate eCRF. The actual dose for each patient will be calculated using a BSA conversion as follows:

Actual dose = planned dose level (mg/m^2) x individual patient (to nearest 10 or 50 mg, BSA higher or lower as appropriate).

Individual patient BSA will be calculated using their height and weight as per standard site procedure. For the purpose of BSA calculations and potential dose readjustment at subsequent cycles, it is acceptable for the BSA to be calculated up to 7 days in advance of Day 1. Dosage adjustments for changes in BSA in subsequent cycles will be made as per standard site practice (e.g., if the BSA changes by ± 10% from the previous dose calculation).

For capsules, individual doses will consist of the minimum number of capsules possible given the available capsule sizes.

[redacted]

The investigator should instruct the patient to take the study drug exactly as prescribed below. All dosages prescribed and dispensed to the patient, and all dose changes during the study must be recorded on the appropriate eCRF.

6.1.1.1 Alternate dosing regimen of LEE011

No alternate dosing regimen of LEE011 is planned.

6.1.2 LEE011 administration

LEE011 may be administered orally in different ways:

1. Capsule: swallow whole or open capsule and pour contents onto semi-solid food or dissolve contents of opened capsule in water or Ora-Sweet (or equivalent) and administer orally or via feeding tube (e.g. nasogastric or gastric)
2. Powder in Bottle (PIB): dissolve powder in water or Ora-Sweet (or equivalent) and administer via feeding tube (e.g. nasogastric or gastric)
3. Liquid formulation.

Since LEE011 shows high solubility across the pH range (> 6 mg/ml at pH 7-9 and > 25 mg/ml at pH 4 or below), the exposure/bioavailability should not be limited by its dissolution rate due to different dosage form of administration. Preliminary in vitro and stability testing support this strategy.

Patients may switch between the different methods of drug administration/formulation depending on clinical status and swallowing abilities. If changes in methods of drug administration/formulation are made during the course of the study and not previously provided to patient, additional PK is recommended as outlined in Tables 7-4 or 7-5. PK and safety will be monitored to ensure that there are no major changes related to methods of LEE011 administration. Detailed instructions regarding preparation and administration of LEE011 capsules, PIB and liquid will be supplied separately to patients/caregivers and investigational sites.

LEE011 should be taken as follows:

- Patients should be instructed to take their once-a-day dose at approximately the same time each day.
- On days when blood for PK samples need to be collected prior to taking study drug, the patient should take the dose in the clinic.
- Each daily dose of LEE011 should be taken with water (preferably one cup) and consumed over as short a time as possible unless otherwise instructed.
- Patients taking capsules should be instructed to swallow capsules whole and to not chew or open them unless otherwise instructed.
- Patients should prepare the dose as described in the Instructions for Use (to be supplied to Investigator sites separate to this protocol).
- Ribociclib can be administered with or without food; however dietary habits around the time of dosing should be as consistent as possible throughout the study.

[redacted]

- On days of PK/PD sampling, every effort must be made to capture the time of any vomiting within 4 hours of drug administration.
- If vomiting occurs during the course of the treatment, then no re-dosing of the patient is allowed before the next scheduled dose.
- Any doses that are missed (not taken within 6 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day.
- Patients should inform the investigational site staff of any missed or delayed doses
- Patients must avoid consumption of grapefruit products, pummelos, star-fruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.

6.1.3 Treatment duration

Patients may continue to receive treatment with LEE011 until disease progression, occurrence of unacceptable toxicity that precludes any further treatment, if treatment is discontinued at the discretion of the investigator, the patient withdraws consent or the patient is enrolled in another Novartis study that can continue to provide LEE011. Patients who have localized disease progression but have evidence of clinical benefit may continue treatment with LEE011 after discussion with Novartis and investigator. Patients who continue on treatment after localized disease progression must discontinue treatment if there is subsequent systemic disease progression.

6.2 Dose escalation guidelines

6.2.1 Starting dose for the dose escalation part

The first cohort of patients in this trial will be treated with a dose of 280 mg/m^2/d, which is 80% of the current well tolerated dose (600 mg/d) in the ongoing adult study [CLEE011X2101] divided by the average adult body surface area (BSA) of 1.72 m^2. Table 6-1 describes the starting dose and the dose levels that may be evaluated during this trial.

Table 6-1 Provisional dose levels

Dose level	Proposed daily dose*	Increment from previous dose	Corresponding adult dose level
-1[c]	210 mg/m^2	-25%	360 mg/d
1 (starting dose)	280 mg/m^2	(starting dose)	480 mg/d
2	420 mg/m^2	50%	720 mg/d
3	630 mg/m^2	50%	1080 mg/d

This table is intended only as a guide. Values in table are examples and actual doses may vary.
* Additional dose levels may be added during the course of the study. Cohorts may be expanded at any dose level below MTD in order to better understand safety, PK or PD.
[c] Dose level -1 is a dose level that may be evaluated if the starting dose level is not well tolerated
Since the adult MTD has not been established, LEE011 doses higher than 630 mg/m^2 may be evaluated depending on the data from the adult Ph1 study and observed safety, PK and PD.

[redacted]

6.2.2 Guidelines for dose escalation and determination of (MTD/ RDE)

For the purposes of dose escalation decisions, 3 to 6 patients will be enrolled in successive cohorts. The first cohort will be treated with the starting dose of 280 mg/m^2/d. Patients must complete a minimum of 1 cycle of treatment with the minimum safety evaluation and drug exposure or have had a DLT within the first cycle of treatment to be considered evaluable for dose escalation decisions. Dose escalation decisions will occur when the cohort of patients has met these criteria. Dose escalation decisions will be made by Investigators and Novartis study personnel. Decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study including safety information, DLTs, all CTCAE grade ≥ 2 toxicity data during Cycle 1, and PK, data from evaluable patients. PK data from patients will be made available on an on-going basis throughout the study and dosing will be adapted accordingly. The recommended dose for the next cohort of patients will be guided by the BLRM with EWOC principle.

The adaptive Bayesian methodology provides an estimate of all dose levels of LEE011 that do not exceed the MTD and incorporates all DLT information at all dose levels for this estimation. In general, the next dose will have the highest chance that the DLT rate will fall in the target interval (16-33%) and will always satisfy the EWOC principle. In all cases, the dose for the next cohort will not exceed a 100% increase from the previous dose. Smaller increases in dose may be recommended by the Investigators and Sponsor upon consideration of all of the available clinical data.

If the first 2 patients in a previously untested dose level experience a DLT, the next cohort will be opened at the next lower dose level or an intermediate dose level (see Table 6-1, Appendix 7). However, if the first 2 patients in a new cohort at a previously tested dose level experience a DLT, further enrollment to that cohort will stop and the BLRM will be updated with this new information. Re-evaluation of the available safety, PK, and PD data will occur.

By incorporating information gained at the preceding dose cohorts, additional patients may be enrolled into this dose cohort only if the dose level still meets the overdose criteria and as agreed by Investigators and Novartis personnel. Alternatively, if recruitment to the same cohort may not resume, a new cohort of patients may be recruited to a lower dose as agreed by Investigators and Novartis personnel and if the BLRM predicts that the risk for this lower dose to exceed the MTD remains below 25% (EWOC).

Dose escalation will continue until identification of the MTD or a suitable lower dose for expansion. This will occur when the following conditions are met:

1. at least 6 patients have been treated at this dose
2. this dose satisfies one of the following conditions:
    a. the posterior probability of targeted toxicity at this dose exceeds 50% and is the highest among potential doses, or
    b. minimum of 12 patients have already been treated on the trial.
3. it is the dose recommended for patients, either per the model or by review of all clinical data by Novartis and Investigators in a dose-escalation teleconference, see Section 6.2.2.1.

To better understand the safety, tolerability and PK of LEE011 additional cohorts of patients may be enrolled at preceding dose levels, or to intermediate dose levels before or while proceeding with further dose escalation.

[redacted]

If a decision is made to escalate to a higher dose level but one or more additional patient(s) treated at the preceding dose level experiences a DLT during the first cycle of treatment, then the BLRM will be updated with this new information before any additional patients are enrolled at that higher dose level. Patients ongoing will continue treatment at their assigned dose levels.

6.2.2.1 Implementation of dose escalation decisions

To implement dose escalation decisions, the available toxicity information (including AEs and laboratory abnormalities that are not DLTs), the recommendations from the BLRM, and the available PK and PD information will all be evaluated by the Investigators and Novartis study personnel (including the study physician and statistician) during a dose decision meeting by teleconference. Drug administration at the next higher dose level may not proceed until the investigator receives written confirmation from Novartis indicating that the results of the previous dose level were evaluated and that it is permissible to proceed to a higher dose level.

Dose escalation will continue until MTD and/or the RDE is reached. The dose for the expansion part will either be the MTD, or a lower dose that is determined to be the RDE.

6.2.2.2 Intra-Patient dose escalation

The starting dose on this study is close to the predicted MTD and therefore, intra-patient dose escalation is not permitted at any time during this study.

6.2.3 Definitions of DLTs

A DLT is defined as an AE or clinically significant abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first 28 days of treatment with LEE011 and meets any of the criteria included in Table 6-2. NCI CTCAE version 4.03 will be used for all grading. For the purpose of dose-escalation decisions, DLTs will be considered and included in the BLRM.

The investigator must notify the Sponsor immediately of any unexpected CTCAE grade ≥ 3 AEs or laboratory abnormalities. Prior to enrolling patients into a higher dose level, CTCAE grade ≥ 2 AEs will be reviewed for all patients at the current dose level.

[redacted]

Table 6-2 Criteria for defining dose-limiting toxicities

TOXICITY	DLT CRITERIA
Hematology	CTCAE grade 4 neutropenia lasting more than 7 consecutive days
	CTCAE grade 4 thrombocytopenia
	CTCAE grade 3 or 4 neutropenia with fever (temperature ≥ 38.5°C)
ECG QT Interval	QTc interval ≥ 501 ms on at least two separate ECGs
Gastro-intestinal	≥ CTCAE grade 3 nausea or vomiting despite optimal anti-emetic therapy ≥ CTCAE grade 3 diarrhea despite optimal anti-diarrhea treatment
Hepato-biliary	≥ CTCAE grade 3 total bilirubin ≥ CTCAE grade 3 ALT (isolated increases in AST without concomitant increases in ALT will not be considered dose-limiting, because of the non-specific nature of AST)
Non-hematologic events	≥ CTCAE grade 3, except for the exclusions noted below
Exceptions to DLT criteria	Grade 3 alopecia
	< 72 hours of CTCAE grade 3 fatigue
	Grade 3 fever or infection without neutropenia < 5 days duration
	Grade 3 laboratory abnormalities that are responsive to oral supplementation or deemed by the investigator to be clinically insignificant
CTCAE version 4.03 will be used for all grading. Optimal therapy for vomiting or diarrhea will be based in institutional guidelines, with consideration of the prohibited medications listed in this protocol.	

6.3 Dose modifications

6.3.1 Dose modification and dose delay

If a patient experiences a DLT, then treatment with LEE011 must be interrupted. For all toxicity grades, if the toxicity resolves to grade 1 or baseline within 1 week of onset, treatment may be resumed at the same or a lower dose level at the investigator's discretion and following discussion with Novartis. For toxicities that result in treatment delays of more than 7 but not more than 21 days, treatment may be resumed at a lower dose level. If a patient requires a dose interruption of > 21 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study. In this event, more frequent follow up as outlined in cycle 1 to monitor this toxicity may be appropriate. Changes to the dose or schedule must be recorded on the Dosage Administration Record eCRF. All patients will be followed for AEs and for SAEs for 30 days following the last dose of LEE011.

Patients who have dose-limiting neutropenia with no other dose-limiting toxicity may receive the same dose in the next cycle with myeloid growth factor support or receive study drug at the next lower dose level. If dose-limiting neutropenia recurs after myeloid growth factor support is added, then the patient should be given the next lowest dose level for subsequent cycles and myeloid growth factor support should be administered.

Patients with extensive involvement of bone marrow who are not evaluable for hematologic toxicity but who have dose-limiting neutropenia should receive the same dose in the next cycle with myeloid growth factor support or receive study drug at the next lower dose level. Since these patients are permitted to have platelet transfusions to meet platelet criteria, no dose modifications will be made for dose-limiting thrombocytopenia.

[redacted]

If a patient experiences an adverse event that is considered to be related to LEE011 that requires interruption of treatment with LEE011, the following must be met in order to resume treatment with LEE011 (except for patients with bone marrow disease):

- ANC must be ≥ 1,000 /µl
- Platelet count must be ≥ 75,000 /µl
- All non-hematologic toxicities must be ≤ grade 1 or returned to baseline
- Absence of any other DLTs, as described in Table 6-2.

6.4 Concomitant medications

Refer to preclinical toxicity and/or clinical data found in the Investigator's Brochure.

6.4.1 Permitted concomitant therapy

Medications required to treat AEs, manage cancer symptoms, concurrent stable diseases and supportive care agents, such as packed red blood cells (PRBC)s, pain medications, anti-emetics and anti-diarrheals are allowed. Stable doses of steroids from study entry and oral contraceptive pills are permitted. The use of any other potential new concomitant medications may be discussed between the investigator and the sponsor on a case by case basis.

Transfusions or growth factor support for white cell counts, platelets or red blood cells are not permitted during Cycle 1, unless the patient has already experienced a DLT. Transfusions and growth factor support should not be used prophylactically during Cycle 1. Patients with bone marrow metastatic disease who are not evaluable for hematological toxicities are exempt.

The patient and/or patient's parent or guardian must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered during the study must be listed on the Concomitant Medications or Significant Non-Drug Therapies eCRF, respectively.

6.4.1.1 Corticosteroids

Chronic dosing of corticosteroids such as dexamethasone and prednisone is known to lead to induction of CYP3A enzymes, thereby potentially increasing the risk of reducing ribociclib drug exposure to subtherapeutic levels. Systemic corticosteroid treatment should not be given during the study, except for:

- Topical applications (e.g., rash), inhaled sprays (e.g., obstructive airways diseases), eye drops or local injections (e.g., intra-articular);
- A short duration (< 5 days) of systemic corticosteroids ≤ to the anti-inflammatory potency of 4 mg dexamethasone (e.g. for chronic obstructive pulmonary disease, or as an antiemetic)

6.4.2 Concomitant therapy requiring caution

The following therapies are permitted in this study, however they should be used with caution:

- Medications that are moderate inhibitors or inducers of CYP3A4/5. (Refer to Appendix 6).

[redacted]

- Sensitive substrates of CYP3A4/5 that do not have a narrow therapeutic index (Refer to Appendix 6).
- Known BSEP inhibitors listed in Appendix 6.
- Agents that are metabolized predominantly by CYP1A2 with a narrow therapeutic index and agents that are strong inhibitors of CYP1A2 listed in Appendix 6.
- Medications that carry a moderate-low risk for QT prolongation listed in Appendix 6.

Patients receiving such medications must be carefully monitored for potentiation of toxicity due to any individual concomitant medication, and may require dose titration of the drug substance.

6.4.3 Prohibited concomitant therapy

The following therapies are prohibited:

- Strong inducers or inhibitors of CYP3A4/5. In particular EIAEDs. (Refer to Appendix 6).
- Substrates of CYP3A4/5 with narrow therapeutic windows (Refer to Appendix 6)
- Medications that carry a strong risk for QT prolongation (Refer to Appendix 6)
- Concurrent anti-neoplastic therapy, including radiotherapy
- Patients should be instructed not to take grapefruit products/juice, or Seville (sour) oranges/juice while receiving LEE011 treatment throughout the study due to its potential for CYP3A4/5 interaction.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Patient Number, that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient Number consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Patient Number available to the investigator through the interface.

6.5.2 Treatment assignment or randomization

The assignment of a patient to a particular cohort will be coordinated by the sponsor. No randomization list will be required for this study.

6.5.3 Treatment blinding

Treatment is not blinded for this study.

6.6 Study drug dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site

[redacted]

personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

LEE011 will be supplied as capsules for oral use of 10, 50, and 200 mg dosage strength. The capsules will be packaged in bottles. LEE011 will also be supplied in Powder in Bottle (PIB) (1200mg in 125mL amber bottle) or in liquid form and will be packaged in bottles.

6.6.1 Study drug packaging and labeling

LEE011 capsules, PIB and liquid form will be packaged in bottles. Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug but no information about the patient. The study drug will be labeled and packaged under the responsibility of the Novartis drug supply management department. The medication will be supplied as open label supply to the sites in a way which allows the patient to take medication at home.

6.6.2 Study drug compliance and accountability

6.6.2.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

Compliance will be assured by administrations of the study treatment under the supervision of investigator or his/her designee, and will be verified by determinations of LEE011 in plasma.

6.6.2.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.6.3 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. Drug supply is to be destroyed at the site only if permitted by local regulations and authorized by Novartis.

[redacted]

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed.

For all visits, there is a ± 3 days window on assessments to take into account scheduling over public or religious holidays if not explicitly specified otherwise. All data obtained from these assessments must be supported in the patient's source documentation. Laboratory assessments that were completed within 72 hours prior to Cycle 1, Day 1 (C1D1) do not need to be repeated.

[redacted]

Table 7-1 Visit evaluation schedule

	Protocol Section	Screening	Treatment Period													EOT	SEC
			Cycle 1					Cycle 2			Cycles 3-6			Subsequent cycles			
Visit Name		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12…**	**22**	**23…**	**777**	**778**
Day of Cycle		**-21 to -1**	**1**	**2**	**8**	**15**	**22**	**1**	**15**	**22**	**1**	**15**	**22**	**1**	**22**	**Last**	**30 day follow-up**
Obtain Main Informed Consent	7.1.1.	X															
Patient History																	
Demography	7.1.1.3.	X															
Inclusion/exclusion criteria	5.2/5.3.	X															
Medical History	7.1.1.3.	X															
Prior Antineoplastic therapies	7.1.1.3.	X															
Diagnosis and extent of cancer	7.1.1.3.	X															
Prior/concomitant medications	6.4.	Continuous															
Physical examination	7.2.2.1.	X	X		X	X	X	X	X		X	X		X		X	
Performance status	7.2.2.4.	X	X					X			X			X		X	
Height, Weight, BSA	7.2.2.3.	X	X					X			X			X		X	
Vital signs	7.2.2.2.	X	X		X	X	X	X	X		X	X		X		X	
Laboratory assessments	7.2.2.5.																
Hematology	7.2.2.5.1.	X	X		X	X	X	X	X		X	X		X		X	
Chemistry	7.2.2.5.2.	X	X		X	X	X	X	X		X	X		X		X	
Thyroid	7.2.2.5.3.	X						X			C4,			C8,		X	

[redacted]

	Protocol Section	Screening	Treatment Period													EOT	SEC
			Cycle 1					Cycle 2			Cycles 3-6			Subsequent cycles			
Visit Name		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12…**	**22**	**23…**	**777**	**778**
Day of Cycle		**-21 to -1**	**1**	**2**	**8**	**15**	**22**	**1**	**15**	**22**	**1**	**15**	**22**	**1**	**22**	**Last**	**30 day follow-up**
											C6			C10,C12, etc.			
Pregnancy test	7.2.2.5.4.	X														X	
Cardiac																	
ECHO	7.2.2.5.6.	X														X	
ECG	7.2.2.5.5.	X	X		X	X	X	X	X		X					X	
Efficacy assessments	7.2.1.																
Tumor evaluation	7.2.1.	X[a]								X			C4, C6		C10, C14, C18, etc.	X	
MIBG imaging (neuroblastoma only)	7.2.1.	X[a]								If positive at Screening			If positive at Screening C4, C6		If positive at Screening C10, C14, C18, etc.	X	
BMA and/or Biopsy (neuroblastoma only)	7.2.1.	X[a]								If positive at Screening			If positive at Screening C4, C6		If positive at Screening C10, C14, C18, etc.	X	
CSF Cytology[b]	7.2.1.	X[a]								If positive at Screening only to confirm CR			If positive at Screening C4, C6 to confirm CR		If positive at Screening C10, C14, C18, etc.to confirm CR		
Safety																	
Adverse events	8.1.	Continuous															
Predictive and Pharmacodynamic	7.2.4.																

[redacted]

Visit Name	Protocol Section	Screening	Treatment Period													EOT	SEC
			Cycle 1					Cycle 2			Cycles 3-6			Subsequent cycles			
		1	2	3	4	5	6	7	8	9	10	11	12…	22	23…	777	778
Day of Cycle		-21 to -1	1	2	8	15	22	1	15	22	1	15	22	1	22	Last	30 day follow-up
Biomarkers																	
Collection of archival tumor blocks/slides	7.2.4.1.	X															
BMA and/or Biopsy (neuroblastoma only)[a]	7.2.4.2.	X								If positive at Screening			If positive at Screening C4, C6		If positive at Screening C10, C14, C18, etc.		
LEE011 administration	6.1.2.		Days 1-21					Days 1-21			Days 1-21			Days 1-21			
PK blood sampling[c]	7.2.3.		X	X[d]	X	X	X	X			C3						
CSF for PK[b]	7.2.3.2.		if available when collected for efficacy assessment or routine/ standard clinical purposes														
Antineoplastic therapies since discontinuation of study treatment	7.1.4.															X	X

[a] Screening window = -28 to- 1 day(s) prior to first dose of LEE011
[b] only for primary CNS (including MRT)
[c] An additional PK blood sample will be required if a patient has CSF collected (see Section 7.2.3.2).
[d] escalation only, C1D2

[redacted]

7.1.1 Screening

The informed consent form (ICF) must be dated and signed prior to any screening procedures not performed as part of the initial diagnostic work-up of the patient are conducted. Once the ICF is signed, all AEs per the descriptions below will be captured in the Adverse Event CRF.

The screening period starts once a patient has provided written informed consent to participate in the study and ends on the day of first dose of LEE011. Screening assessments have to be done within 21 days prior to the first dose of LEE011 except for baseline tumor imaging scans, CSF cytology, and bone marrow aspirates and/or biopsies which may be done within 28 days prior to the first dose of LEE011 and/or hematologic (ANC, platelet count, and hematocrit) inclusion criteria within 7 days prior to first dose of LEE011.

7.1.1.1 Eligibility screening

The procedures for eligibility check, patient identification number assignments, and coordination among the sites involved will be provided in a separate document prior to study start.

7.1.1.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Log eCRF, and each patient's demographic information will be added on the Demography eCRF. No other data will be entered into the clinical database for screen failure patients.

7.1.1.3 Patient demographics and other baseline characteristics

The data that will be collected on patient characteristics at baseline include general demographics, relevant medical history, the diagnosis and extent of their tumor(s) and prior antineoplastic therapies.

7.1.2 Treatment period

The treatment period commences on the first day of the first cycle (C1D1) of LEE011 and ends after the last dose of LEE011.

Patients who enter the study will be treated with daily dosing of oral LEE011 for 21 consecutive days followed by a 7 day planned break until the patient experiences unacceptable toxicity that precludes any further treatment, disease progression, and/or treatment is discontinued at the discretion of the investigator or by patient's premature withdrawal.

During the study treatment period, patients will be regularly monitored to assess the safety and early anti-tumor activity of the treatment. For the purpose of scheduling and evaluations, a treatment cycle will consist of 28 days.

For details of assessments during the treatment period, refer to Table 7-1.

[redacted]

7.1.3 End of treatment (EOT) visit

At any time, patients may voluntarily withdraw from the study or be removed from it at the discretion of the investigator. If withdrawal occurs, or if the patient fails to return for visits, effectively withdrawing, the investigator must determine the primary reason for a patient's premature withdrawal, record this information on the End of Treatment eCRF, and notify Novartis. Patients may be withdrawn from study treatment for one of the following reasons:

1. Adverse event(s)
2. Disease progression
3. Protocol violation/deviation
4. Patient withdrew consent
5. Lost to follow-up
6. Death
7. Transfer to another Novartis clinical study that continues to provide LEE011.

Patients who discontinue study treatment for any of the above reasons (except death) should be scheduled for an EOT visit within 14 days of permanently discontinuing LEE011 at which time all of the assessments listed for the EOT visit will be performed. An EOT eCRF will be completed, giving the date and reason for stopping the study treatment.

The EOT completion evaluations are outlined in Table 7-1.

All patients who discontinue study treatment, including those who refuse to return for a final visit, should be contacted 30 days after discontinuing study drug for safety evaluations and a list of antineoplastic therapies received since discontinuation. See Section 7.1.4. A Study Evaluation Completion (SEC) eCRF will then be completed, giving the date and reason for study discontinuation.

For patients who refuse to return for visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone. Patients lost to follow up should be recorded as such on the SEC eCRF. A patient is considered "lost-to-follow up" if the patient fails to show up for a scheduled follow-up visit and no response despite at least 3 documented failed attempts to contact the patient, such as via phone calls and/or registered letters. The investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

Patients that transition into the rollover clinical trial will perform end of treatment procedures. However, follow-up for safety, survival and disease progression will not be performed.

7.1.3.1 Patient replacement

Escalation part:

Patients will not be replaced on study. However, if a patient is considered as non-evaluable for the DDS, enrollment of a new patient to the current cohort will be considered if there is less than the required number of evaluable patients. Minimum and maximum numbers of evaluable patients per cohort are defined in Section 6.2.2.

[redacted]

Expansion part:

Patients will not be replaced.

7.1.4 Follow-up period

All patients will have safety evaluations completed 30 days after the last dose of LEE011. At this time AE, SAE and concomitant medications (including subsequent antineoplastic therapy) information during the follow-up period will be recorded on the AE eCRF and Novartis will be informed as necessary. For eCRF purposes, this will be referred to a Study Evaluation Completion (SEC).

Patients lost to follow-up should have this documented on the appropriate eCRF and attempts made to contact the patient to ascertain the reason and required study information, as described in Section 7.1.3.

7.2 Assessment types

7.2.1 Efficacy assessments

All patients will have disease response assessment per RECIST v1.1 (Appendix 1). Patients with primary CNS tumors (including MRT) will have response assessment per RANO criteria (Appendix 3) whenever possible, in addition to RECIST. Disease response in neuroblastoma patients will be assessed per INRC (Appendix 2) whenever possible in addition to RECIST. Response assessments for patients with MIBG-positive disease and bone marrow-positive disease will also be done when applicable, per standard institutional practice. Disease response and progression will be determined locally by the investigator. All imaging procedures at screening must be completed within 28 days of the first dose of LEE011.

For patients with primary CNS (including MRT), the method of measurement should follow the neuro-oncology criteria of tumor response using 2-dimensional and volumetric measurements (if available) on gadolinium chelate-enhanced brain tumor magnetic resonance imaging (Gd-MRI) (Appendix 3). All Gd-MRIs (standard brain tumor magnetic resonance imaging [MRI] including both pre-contrast and post-contrast images using a Gadolinium (Gd) chelate as the contrast agent) should be performed when the patient is on a non-increasing dose of corticosteroids for at least 7 days.

For patients with non-CNS tumors, the method of measurement should follow standard practice (ie, computed tomography [CT] or MRI scans) and response will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Appendix 1). Patients with neuroblastoma will undergo MIBG scanning, and bone marrow aspirate and/or biopsy for presence of disease per standard institutional practice at screening. The use of ^{123}I for MIBG imaging is recommended for all scans. MIBG scans and bone marrow aspirates and/or biopsies should be performed within 28 days of the first dose of LEE011. Visible skin lesions and easily palpable subcutaneous tumors may be measured by physical examination using a ruler or calipers. Ultrasound should not be used to measure tumor lesions.

Each lesion that is measured at baseline (screening), must be measured by the same method throughout the study so that the comparison is consistent.

Antitumor activity in patients with non-measurable disease will only be noted.

[redacted]

Subsequent tumor evaluations will be performed on Day 22 (±7 days) of cycles 2, 4 and 6. After cycle 6 tumor evaluations will be performed on Day 22 (±7 days) of every 4th cycle (e.g., C10, C14, C18), or sooner if there is clinical evidence of disease progression. Tumor evaluations will also be performed at EOT. If the last prior tumor evaluation was within 28 days of EOT or objective evidence of progressive disease has already been documented, then tumor evaluations do not need to be repeated at EOT.

Tumor evaluations after the screening assessment will include evaluation of all sites of disease identified at baseline, using the same technique that was used at screening. If there was no evidence of disease in a body region at screening, that region does not need to be imaged at subsequent assessments, unless there is clinical concern for a new lesion in that body region. Bone marrow aspirate and/or biopsies and MIBG scans are not required after baseline if they were negative at screening.

The CSF test is required for primary CNS tumors (including MRT) patients at screening and is performed per institutional standards. If sampling is not feasible, patients may still enroll in study after discussion with Novartis and the investigator. Information will be collected if performed. CSF will be performed at Screening and if positive at screening, subsequent measurements are performed only for confirmation of CR as needed on Day 22 (±7 days) of cycles 2, 4 and 6. After cycle 6 tumor evaluations, CSF test will be performed as needed on Day 22 (±7 days) of every 4th cycle (e.g., C10, C14, C18), or sooner if there is clinical evidence of disease progression. Only 2 negative sequential CSF cytology are required for establishing CR.

All radiological assessments obtained for all patients enrolled during the study will be centrally collected and subjected to quality checks by an imaging CRO selected by Novartis. The site manual provided by the designated imaging CRO will provide further details regarding image collection.

7.2.2 Safety and tolerability

Safety and tolerability assessments will include adverse event reporting and changes from baseline in laboratory measures and vital signs. Tolerability will be assessed by the incidence of AEs leading to study drug delay or discontinuation. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

A full physical examination (PE) that evaluates all major organ systems will be performed at screening. This should include a complete neurological exam. Subsequent PEs should be focused on sites of disease, and clinical signs and symptoms. Patients with CNS disease and baseline neurologic findings should have a complete neurologic exam performed at all subsequent visits.

Significant findings that were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF.

PEs to be performed are outlined in Table 7-1.

[redacted]

7.2.2.2 Vital signs

Vital signs (heart rate, blood pressure and temperature) will be obtained in the same position, either sitting or supine, as appropriate prior to any blood collection.

Vital signs to be obtained are outlined in Table 7-1.

7.2.2.3 Height, weight and body surface area (BSA)

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. Sitting height should be measured when appropriate. BSA will be measured using the patient's weight and height, in accordance with local site procedure. For the purpose of BSA calculations and potential dose readjustment at subsequent cycles, it is acceptable for the BSA to be calculated up to 7 days in advance of Day 1.

Assessments to be obtained are outlined in Table 7-1.

7.2.2.4 Performance status

Performance status will be scored using the Karnofsky (for patients greater than 16 years old) or Lansky (for patients less than or equal to 16 years old) performance scales, depending on the patient's age (see Appendix 4 and Appendix 5).

Performance status to be obtained are outlined in Table 7-1.

For patients that have their 17th birthday during the study, performance status will continue to be assessed by the Lansky scale, in order to preserve continuity.

7.2.2.5 Laboratory evaluations

Laboratory tests will be collected and analyzed by the study site's local laboratory. More frequent examinations may be performed at the investigator's discretion if medically indicated and should be recorded on the Unscheduled Visit eCRFs.

At any time during the study, abnormal laboratory parameters which are clinically relevant (e.g., require dose modification and/or interruption of study drug, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, must be recorded in the AE eCRF.

Novartis will be provided with a copy of the laboratory certification and tabulation of the normal ranges for each parameter required. In addition, if at any time a patient has laboratory parameters obtained from a different outside laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges for that laboratory.

For all visits, there is a ± 3 days window on assessments to take into account scheduling over public or religious holidays if not explicitly specified otherwise. Laboratory assessments that were completed within 72 hours of C1D1 do not need to be repeated.

7.2.2.5.1 Hematology

Please refer to Table 7-2 for a list of tests to be performed.

For timing of assessments, refer to Table 7-1.

[redacted]

7.2.2.5.2 Clinical chemistry

Please refer to Table 7-2 for a list of tests to be performed.

For timing of assessments, refer to Table 7-1.

7.2.2.5.3 Thyroid

Please refer to Table 7-2 for a list of tests to be performed. TSH is required at all required timepoints. If TSH is abnormal, T3 and free T4 should be performed.

For timing of assessments, refer to Table 7-1.

Table 7-2 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Complete blood count (CBC) with differential - white blood cell (WBC) count, absolute neutrophil count [including bands], lymphocyte, monocyte, eosinophil, and basophil counts, hemoglobin, hematocrit, and platelet count.
Chemistry	Sodium, potassium, chloride, bicarbonate, urea or BUN, creatinine, glucose, AST (SGOT), ALT (SGPT), total bilirubin (if a total bilirubin elevation ≥ grade 2 occurs then direct and indirect bilirubin should be measured), LDH, albumin, calcium, magnesium, alkaline phosphatase (ALP), and phosphate.
Thyroid	TSH. If TSH abnormal, T3 and free T4 to be performed.

7.2.2.5.4 Pregnancy assessments

When effective contraception is required pregnancy testing is required at screening and at the end of the trial. At screening a serum pregnancy test should be performed, while at the end of trial urinary pregnancy tests are sufficient.

Pregnancy test to be performed:

- Screening (serum)
- End of treatment (urine or serum)

A positive pregnancy test is cause for immediate withdrawal.

For females to be considered “of non-childbearing potential”, patient should meet one of the following:

- Prior to onset of menarche (pre-menarche)
- Surgically sterile for at least 6 months (hysterectomy with bilateral oophorectomy or tubal ligation). Documentation of sterilization method must be provided. The date of sterilization will be recorded.

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology (DS&E) follow-up should be recorded on the same form and should include an assessment of the possible relationship to

[redacted]

the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.2.2.5.5 Electrocardiogram (ECG)

A standard 12-lead ECG in triplicate will be performed after the patient has been resting for 5-10 min prior to each time point indicated in Table 7-3. Each ECG recording must be taken at a minimum of 2-minute intervals. The combined QTc values from these 3 ECGs will be averaged to provide a single value for each patient.

If an abnormal ECG is obtained at any time, patient's electrolytes must be reviewed and repeat ECG measurements must be done after correction of electrolyte abnormalities.

All ECGs will be transmitted to a central laboratory and will be centrally reviewed by an independent reviewer.

In the event that a QTc value of ≥ 501 ms is observed, a blood sample for PK will be collected to determine plasma levels of LEE011 and any other identified metabolites.

Each ECG tracing should be labeled with the study number, patient initials, patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities at screening should be recorded on the relevant medical history/current medical conditions eCRF page. Only clinically significant abnormalities will be recorded in the AE eCRF page.

Table 7-3 Central ECG collection plan

Cycle	Day	Time
Screening		Anytime during the screening period
1	1	pre-dose
1	1	1h post-dose (± 15 min)
1	1	2h post-dose (± 15 min)
1	1	4h post-dose (± 30 min)
1	8	pre-dose
1	8	2h post-dose (± 15 min)
1	8	4h post-dose (± 30 min)
1	8	6h post-dose (± 30 min)
1	15	pre-dose
1	15	2h post-dose (± 15 min)
1	15	4h post-dose (± 30 min)
1	15	6h post-dose (± 30 min)
1	22	Anytime during visit
2	1	pre-dose
2	15	Anytime during visit
3-6	1	Anytime during visit
Unscheduled		As clinically indicated
EOT		Within 14 days of last dose

7.2.2.5.6 Cardiac imaging - echocardiogram (ECHO)

Cardiac imaging by ECHO to be performed are outlined in Table 7-1.

[redacted]

7.2.3 Pharmacokinetics

7.2.3.1 PK blood sample collection and handling

All blood samples will be taken either by direct venipuncture or through an indwelling cannula (eg, inserted in a forearm vein, or central venous line) according to the dose escalation schedule described in Table 7-4 and, for the dose expansion schedule Table 7-5. Residual plasma samples after the PK concentration analysis may be used for drug metabolism investigations.

At the specified time points, 1 mL of blood will be collected in tubes containing K3 EDTA. Refer to the Laboratory Manual for detailed instructions for the collection, handling and shipping of samples.

Patients may switch between the different methods of drug administration/formulation depending on clinical status and swallowing abilities. If changes in methods of drug administration/formulation are made during the course of the study and not previously provided to patient, PK will be collected as outlined in Tables 7-4 or 7-5. These subjects should have one set of PK blood samples collected at pre-dose, 2 hours post-dose and 4 hours post-dose at the time of the first dose using the new method of administration or formulation. PK and safety will be monitored to ensure that there are no major changes related to methods of LEE011 administration.

Table 7-4 Pharmacokinetic blood collection log – dose escalation part

Cycle	Day	Scheduled time points* (hours)
1	1	pre-dose
1	1	1h post-dose (± 15 min)
1	1	2h post-dose (± 15 min)
1	1	4h post-dose (± 30 min)
1	1	8h post-dose (± 30 min)
1	2	24h post dose (± 1 h, pre-dose for the next dose)
1	8	pre-dose
1	8	2h post-dose (± 15 min)
1	15	pre-dose
1	15	1h post-dose (± 15 min)
1	15	2h post-dose (± 15 min)
1	15	4h post-dose (± 30 min)
1	15	8h post-dose (± 30 min)
1	22	24h post day 21 dose (± 1 h)
2	1	pre-dose
2	1	4h post-dose (± 30 min)
3	1	pre-dose
Unscheduled		PK samples related to a QTc >= 501 ms
Unscheduled[a]		When CSF is collected
Not applicable (NA)	NA	pre-dose[b]
Not applicable	NA	2h post-dose (± 15 min)[b]
Not applicable	NA	4h post-dose (± 30 min)[b]
Unscheduled		Anytime

[redacted]

Cycle	Day	Scheduled time points* (hours)
*All measurement times are relative to dose of LEE011 unless otherwise specified. a. A PK blood sample (1 mL) should be obtained at the same time point a CSF sample is obtained. b. For drug administration/ formulation switch not previously provided to patient, one set of PK blood samples should be collected at the time of the first dose using the new administration or formulation.		

Table 7-5 Pharmacokinetic blood collection log – dose expansion part

Cycle	Day	Scheduled time points* (hours)
1	1	pre-dose
1	1	4h post-dose (± 30 min)
1	8	pre-dose
1	15	pre-dose
1	22	24h post day 21 dose (± 1 h)
2	1	pre-dose
3	1	pre-dose
Unscheduled		PK samples related to a QTc >= 501 ms
Unscheduled[a.]		When CSF is collected
NA	NA	pre-dose[b]
NA	NA	4h post-dose (± 30 min)[b]
Unscheduled		Anytime
*All measurement times are relative to dose of LEE011 unless otherwise specified. a. A PK blood sample (1 mL) should be obtained at the same time point a CSF sample is obtained. b. For drug administration/ formulation switch not previously provided to patient, one set of PK blood samples should be collected at the time of the first dose using the new administration or formulation.		

7.2.3.2 PK cerebrospinal fluid (CSF) sample collection and handling

If CSF is collected as part of efficacy assessment or routine/standard care at any time after patient has received first dose of LEE011, a sample will be requested for assaying LEE011 concentration levels (maximum 2 mL volume). As the timing of this procedure may vary depending on clinical condition of the patient, there is no set time point(s) for this measurement.

CSF samples should be processed, labeled, and stored as specified in the Laboratory Manual. The actual sample collection date and time should be entered on the appropriate eCRF.

When CSF is obtained, a PK blood sample (1 mL) is required at the same time point for plasma concentration analysis. Tmax for LEE011 is around 2-4 hours and SS is reached in about 8 days. Therefore, recommended timing for CSF and PK sampling is after 8 days of continuous treatment and within 2-5 hours after dosing with LEE011.

7.2.3.3 Analytical method

The plasma and CSF samples from all patients will be assayed for concentrations of LEE011 and if needed, any clinically significant identified metabolites using a validated liquid chromatography-tandem mass spectrometry assay (LC/MS/MS). Residual samples may be used for drug metabolism investigations. Values below the lower limit of quantification (LLOQ) of approximately 5.00 ng/mL or lower will be reported as 0 ng/mL. Missing values will be labeled accordingly.

[redacted]

7.2.4 Biomarker assessments

7.2.4.1 Potential predictive biomarkers

All patients will be required to provide archival tumor samples (at diagnosis or relapse) unless otherwise agreed upon by Novartis and the investigator. The accompanying pathology report should also be included. [redacted]

7.2.4.2 Pharmacodynamic biomarkers

Patients with bone marrow involvement at study entry will provide pre- and post-treatment bone marrow samples (BMA and/or biopsy) for efficacy assessments. Remaining samples will be analyzed for changes in key pharmacodynamic markers e.g. [redacted] and [redacted]. If bone marrow aspirate/biopsy is being collected on a day when LEE011 is administered, every effort should be made to obtain BMA/biopsy sample around 4 hours post dose.

Additional markers may be analyzed if indicated by new findings from the literature as well as from Novartis internal data.

Detailed instructions for the collection, handling, and shipping of biomarker samples are outlined in the Laboratory Manual.

Table 7-6 Biomarker sample collection plan

Sample Type	Visit	Biomarker Analysis	Purpose
Archival Tumor (at diagnosis or relapse)	Screening (Anytime)	[redacted]	Potential predictive markers
Bone Marrow Aspirate (neuroblastoma patients only, if feasible)	Screening, C2D22, additional samples from other cycles, if feasible	[redacted]	PD analysis
Bone Marrow Biopsy (neuroblastoma patients only, if feasible)	Screening, C2D22, additional samples from other cycles, if feasible	[redacted]	PD analysis

7.2.4.3 Storage of remaining biomarkers samples and additional analyses

The remaining biomarker samples (tumor, bone marrow aspirate or biopsy) may be stored for up to 15 years and further analyzed to address scientific questions related to the LEE011 and/or cancer and/or the development of biological tests. The storage of these biomarker samples for additional analyses is optional. A decision to perform such exploratory biomarker research studies would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

[redacted]

Samples will only be stored and additional analyses will only be performed on samples from patients who agree to participate in this biomarker component by agreeing to this option in the main informed consent form.

7.2.5 Total blood volume

The total volume of blood that will be drawn from each patient in this study during the first 2 cycles (8 weeks) of treatment is shown in Table 7-7.

Table 7-7 Maximum total blood volume (pediatric patients)

	Maximum Sample Volume	24 hr (Cycle 1 Day 1)		Cycle 1 (4 weeks)		Cycle 1 + 2 (8 weeks)	
		No. samples	Total volume	No. samples	Total volume	No. samples	Total volume
Hematology	1 mL	1	1 mL	4	4 mL	6	6 mL
Chemistry	1 mL	1	1 mL	4	4 mL	6	6 mL
Thyroid	1 mL	0	0 mL	0	0 mL	1	1 mL
PK	1 mL	5	5 mL	14	14 mL	16	16 mL
Total			7 mL	22 mL	22 mL	32	32 mL
For younger and/or smaller patients where collection of these samples may compromise local blood volume limits, priority for blood samples will be (1) safety, followed by (2) PK							

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Except for screening failures, adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Relevant Medical History/Current Medical Conditions page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to grades 1 - 4, will be

[redacted]

used. CTCAE grade 5 (death) will not be used in this study; rather, information about deaths will be collected through the End of Treatment or Study Evaluation Forms.

The occurrence of adverse events should be sought by non-directive questioning of the patient during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE grade 1-4)
2. Its duration (Start and end dates or Ongoing at End of Study.
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a SAE is defined as in Section 8.2.1.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per INRC and RECIST for neuroblastoma, RANO and RECIST for primary CNS (including MRT) and RECIST criteria for all solid tumors), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

[redacted]

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.2 Serious adverse events

8.2.1 Definitions

SAE is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each

[redacted]

specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis DS&E department.

The telephone and telefax number of the contact persons in the local department of DS&E, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form (CRF) documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure (IB) or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis DS&E department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis DS&E. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8.4 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

[redacted]

9 Data collection and management

9.1 Data confidentiality

Information about study patients will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed patient authorization informing the patient of the following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research patient to revoke their authorization for use of their PHI.

In the event that a patient revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the patient experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO [Contract Research Organization]) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

[redacted]

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol including biomarker and PK data into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

In addition to data entered into eCRFs, requisition forms may also need to be completed for biomarker and PK sample collection. Imaging data from the patients enrolled in the study will be collected from the Investigator sites, sent to a specialty CRO, and held centrally.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

The data will be analyzed by Novartis and/or designated CRO.

It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant PK and PD measurements using descriptive statistics (quantitative data) and contingency tables (qualitative data).

The study data will be analyzed and reported based on all patients' data of the dose escalation and expansion parts up to the time when all patients have potentially completed at least six cycles of treatment or discontinued the study. Any additional data for patients continuing to

receive study treatment past the data cutoff date for the primary CSR, as allowed by the protocol, will be reported once all patients have discontinued the study.

Unless otherwise specified, cohorts treated during the dose escalation/dose expansion with the same dose levels of LEE011 will be pooled into a single treatment group and all summaries, listings, figures and analyses will be performed by treatment group.

10.1 Analysis sets

10.1.1 Full analysis set

The FAS includes all patients who received at least one dose of LEE011. Patients will be classified according to the planned treatment. The FAS will be used for all listings of raw data. Unless otherwise specified the FAS will be the default analysis set used for all analyses.

10.1.2 Safety set

The safety set includes all patients who received at least one dose of LEE011, and have at least one valid post-baseline safety assessment. The statement that a patient had no AEs (on the AE eCRF) constitutes a valid safety assessment. Patients will be classified according to treatment received, where treatment received is defined as:

1. The treatment assigned if it was received at least once, or
2. The first treatment received in the study if the assigned treatment was never received.

10.1.3 Dose-determining analysis set

The dose-determining set consists of all patients from the safety set who either meet the following minimum exposure criterion and have scheduled safety evaluations, or experience a DLT. A patient is considered to have met the minimum exposure criterion if he received at least 16 out of the 21 planned daily doses (3 weeks on, 1 week of schedule) of LEE011 in the first 28 days of dosing.

Patients who do not experience DLT during the first cycle are considered to have sufficient safety evaluations if they have been observed for $\geq$ 28 days following the first dose, and are considered by both the Sponsor and Investigators to have enough safety data to conclude that a DLT did not occur.

Patients who do not meet these minimum safety evaluation requirements will be regarded as ineligible for the DDS.

10.1.4 Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of all patients who have at least one blood sample providing evaluable drug concentration data. The PAS will be used for summaries of PK data (Tables and Figures) as well as for listings of derived parameters.

Note: Patients will be removed from the estimation of certain PK parameters on an individual basis depending on the number of available blood samples. These patients will be identified at the time of the analyses and prior database lock.

[redacted]

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including age, gender, height, weight, medical condition, disease characteristics, etc. will be summarized descriptively for all patients in the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

10.3 Treatments (study treatment, concomitant therapies, compliance)

10.3.1 Study treatment

The actual dose and duration in days of LEE011 treatment as well as the dose intensity (computed as the ratio of actual dose received and actual duration) and the relative dose intensity (computed as the ratio of dose intensity and planned dose received/planned duration), will be listed and summarized.

The summary data will be presented for each treatment cycle individually, as well as for all study days as a single category.

10.3.2 Concomitant therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug treatment will be listed by patient and summarized by ATC term by means of contingency tables.

10.3.3 Compliance

Compliance to the protocol will be assessed by the number and proportion of patients with protocol deviations. These will be identified prior to database lock and will be listed and summarized.

10.4 Primary objective

The primary objective of the study is to estimate the MTD and/or the RDE of LEE011 when administered as a single agent orally in patients. The corresponding primary analysis method is an adaptive BLRM guided by the EWOC principle (Neuenschwander et al 2008).

10.4.1 Variable

The primary endpoint is the incidence of DLTs in cycle 1. Estimation of the MTD of the treatment will be based upon the estimation of the probability of DLT in Cycle 1 for patients in the DDS. This probability is estimated by the model in Section 10.4.2.

10.4.2 Statistical hypothesis, model, and method of analysis

An adaptive BLRM with 2 parameters, guided by the EWOC principle, will be used to make dose recommendations and estimate the MTD/ RDE during the study. The use of Bayesian response adaptive models for Phase I studies has been advocated by the EMEA guideline on

[redacted]

small populations 2006 and by Rogatko et al (2007) and is one of the key elements of the FDA's Critical Path Initiative.

The adaptive BLRM model will be fitted on the dose-limiting data (i.e. absence or presence of DLT) accumulated in cycle 1 throughout the dose escalation part (and possibly during the dose expansion part), for modeling the dose-DLT relationship of LEE011.

The DLT relationship in the escalation part of the study will be described by the following Bayesian logistic regression model:

$$\text{logit}(\pi_{(d)}) = \log(\alpha) + \beta \log(d/d^*), \qquad \alpha>0, \beta>0$$

where $\text{logit}(\pi_{(d)})= \ln (\pi_{(d)}/(1-\pi_{(d)}))$, and $\pi_{(d)}$ is the probability of a DLT at dose d. Doses are rescaled as d/d* with reference dose of $d^*= 580$ mg/m^2. As a consequence α is equal to the odds of the probability of toxicity at d*. Note that for a dose equal to zero, the probability of toxicity is zero.

If a different dosing schedule will be considered, a Bayesian Meta-analytic approach will be used to take into account historical data collected for the initially planned schedule in the actual study, in order to derive an informative prior estimation of the dose-toxicity relationship for the new dosing regimen. This informative prior will be combined with DLT data for the new dosing regimen using a 2-parameter BLRM.

For further details of the statistical model including specification of prior distribution for the BLRM parameters, implementation and results under a variety of data scenarios please refer to Appendix 7.

Dose recommendation

Dose escalation

After each cohort of patients, the posterior distributions for the probabilities of DLT rates at different dose levels are obtained. The results of this analysis are summarized in terms of the estimated probabilities that the true rate of DLT at each dose-level will lie within each of the following intervals:

- [0, 0.166) under-dosing
- [0.166, 0.333) targeted toxicity
- [0.333, 1.00] excessive toxicity

The overdose control criterion mandates that any dose of LEE011 for which the DLT rate has more than a 25% chance of being excessively toxic, i.e. exceeding 0.333, will not be considered for the next dose cohort. The final estimate of the MTD/RDE before the start of the expansion will also satisfy this condition.

Note that the dose that maximizes the posterior probability of targeted toxicity is the best estimate of the MTD, but it may not be an admissible dose according to the overdose criterion if the amount of data is insufficient. If vague prior information is used for the probabilities of DLT, in the early stages of the study this escalation procedure will reflect a conservative strategy.

[redacted]

Details of the criteria for dose escalation and the determination of the MTD are provided in Section 6.2.2.

Dose expansion

Upon completion of the first cycle of treatment for at least 10 patients within the dose expansion part, if the observed DLT rate exceeds 33%, the BLRM will be re-run to confirm that the estimated MTD/RDE still satisfies the overdose criterion. If the dose fails to satisfy the criterion a change to the dose under study may be made according to the Bayesian model recommendation, after review of the clinical data.

Listing/ summary of DLTs

DLTs will be listed and their incidence summarized by primary system organ class, worst grade based on the CTCAE version 4.03, type of adverse event, and by treatment group. The dose-determining set will be used for these summaries.

10.4.3 Handling of missing values/censoring/discontinuations

Continuing events (e.g. AEs, concomitant medication, etc.) will be summarized using the data cut-off date as the date of completion, with an indication within listings that the event is continuing. For patients who discontinue the study with ongoing events, the discontinuation date will be used as the completion date of the event with the appropriate censoring as described in the above paragraph.

The reason for discontinuation from study will be summarized and listed, along with dates of first and last study drug treatment, duration of exposure to study drug treatment and date of discontinuation for each patient.

Other missing data will simply be noted as missing on appropriate tables/listings.

10.4.4 Supportive analyses

Supportive analyses may be performed to incorporate later cycle DLT data to provide additional guidance for dose escalation within the escalation part of the study.

Additional exploratory and supportive analyses will be conducted if appropriate and defined in the reporting and analysis plan (RAP).

10.5 Secondary objectives

Refer to Section 3 for secondary objectives of dose escalation part and dose expansion part.

10.5.1 Population and grouping for the analyses

For all safety analyses, the safety population will be used. All other secondary analyses will use the population specified in the relevant section below. All listings and tables will be presented by treatment group (or study arm for efficacy analysis in the expansion part with patients classified to treatment group as described in Section 10.

[redacted]

10.5.2 Safety evaluation

10.5.2.1 Analysis set and grouping for the analyses

The overall observation period will be divided into three mutually exclusive segments:

1. Pre-treatment period: from day of patient's informed consent to the day before first dose of study medication.
2. On-treatment period: from day of first dose of study medication to 30 days after last dose of study medication.
3. Post-treatment period: starting at day 31 after last dose of study medication.

10.5.2.2 Adverse events (AEs)

All adverse events recorded during the study will be summarized. The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by primary system organ class, severity based on the CTCAE version 4.03, type of adverse event, and relationship to the study drug by treatment group. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by primary system organ class, type of adverse event, and by treatment group.

Any other information collected (e.g. start/end dates and duration of adverse event, severity or relatedness to study medication) will be listed as appropriate.

10.5.2.3 Laboratory abnormalities

All laboratory values will be converted into SI units, as appropriate, and the severity grade calculated using CTCAE, version 4.03. Parameters for which a grading does not exist will be classified into low/normal/high group by means of laboratory normal ranges.

For each laboratory test (e.g. hematology, biochemistry, etc.) a listing of laboratory values will be provided by laboratory parameter, patient and treatment group. The frequency of notable lab abnormalities will be displayed by parameter, cycle and treatment group. Similarly, the frequency of all laboratory abnormalities will be displayed by parameter, worst CTCAE version 4.03 grade experienced and treatment group. A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTC grade 3 or 4 laboratory toxicities).

Laboratory data will be summarized by presenting grade shift tables for those parameters for which CTCAE version 4.03 allows classification. All remaining data will be summarized by presenting shift tables based on normal ranges.

Laboratory data will also be displayed by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges).

10.5.2.4 Electrocardiograms

Data from electrocardiograms will be listed, notable values will be flagged and any other information collected will be listed as appropriate. Furthermore, combined QTc values from the triplicate ECGs will be averaged to provide a single value for each patient and to be used in the summary tables.

[redacted]

Change from baseline in QT intervals by treatment will be summarized for each visit. Moreover change from baseline in all ECG parameters for the worst change from baseline will be summarized. The frequency and percentage of patients with notable ECGs and newly occurring qualitative ECG abnormalities will be tabulated by treatment group and mutually exclusive categories of QTcF, QTcB, QT, HR, PR, QRS (see Table 10-1).

In the listings of baseline cardiac imaging results subjects with a notable post-dose QTc abnormality will be identified.

Table 10-1 ECG parameters and abnormal values

ECG Parameter	Abnormal values
QT, QTcF and QTcB	New absolute values >450, >480 and >500
	Changes from baseline >30 and >60
HR	Decrease from baseline >25% and to a HR < 50
	Increase from baseline >25% and to a HR > 100
PR	Increase from baseline >25% and to a value >200
QRS	Increase from baseline >25% and to a value >110

QT or QTc values will also be also considered notable when >450 msec, >480 msec and > 500 msec. They will be flagged as such in listings.

The difference between baseline and maximum post-QTcF values will also be summarized. Post-baseline values will also be presented in the following categories: an increase from baseline of > 30 msec or > 60 msec, or new absolute values > 450 msec, > 480 msec, or > 500 msec. A frequency table for such categories will be summarized by treatment.

A listing of QT prolonging concomitant medications will be produced.

Additional outputs and details will be fully specified in the RAP.

10.5.2.5 Other safety data

Data from other tests (e.g., vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

10.5.2.6 Supportive analyses for secondary objectives

Additional exploratory and supportive analysis will be conducted if necessary and specified in the RAP.

10.5.3 Tolerability

Tolerability of study drug LEE011 will be assessed by summarizing the number of dose interruptions and dose reductions. Reasons for dose interruption and dose reductions will be listed by patient and summarized. Cumulative dose, dose intensity and relative dose intensity of LEE011 will be listed by patient and summarized. Categories for relative dose intensity of LEE011 will be specified as < 0.5, ≥ 0.5 - < 0.75, ≥ 0.75- < 0.9, ≥ 0.9-< 1.1, ≥ 1.1. The number and proportion of patients within each category will be presented.

[redacted]

10.5.4 Efficacy evaluation

Assessment of preliminary efficacy for all patients will be based on RECIST v1.1 (Appendix 1). In addition, patients with primary CNS tumors (including MRT) will have response assessment per RANO criteria (Appendix 3) whenever possible. Disease response in Neuroblastoma patients will additionally be assessed per INRC (Appendix 2).

TTP and DOR per RECIST v1.1 will be presented descriptively for the neuroblastoma and the MRT arms in the expansion phase using a Kaplan-Meier curve. Summary statistics from the Kaplan-Meier distribution will be determined, including the median and estimates at 4 and 8 months, for TTP and DOR respectively. These statistics will be provided as point estimates with 95% confidence intervals.

ORR as per RECIST v1.1 will be presented at the MTD/RDE as point estimate and corresponding 95% exact confidence interval according to Clopper-Pearson for the neuroblastoma and the MRT population separately.

The same analysis will also be presented as per RANO in MRT patients and as per INRC in Neuroblastoma patients.

Moreover, preliminary efficacy response as per RECIST 1.1 will be listed for all patients as well as preliminary efficacy response per RANO and INRC for patients with Primary CNS and with Neuroblastoma, respectively.

Any other additional analysis will be fully specified in the RAP.

10.5.5 Pharmacokinetics

All patients in PAS will be included in the PK data analysis.

Pharmacokinetic variables:

The PK parameters listed in Table 10-2 for LEE011 will be estimated and reported as appropriate from the individual plasma concentration versus time profiles using a non-compartmental approach within Phoenix® (Pharsight, Mountain View, CA). Exploratory PK analysis will be conducted using compartmental modeling as required.

Table 10-2 Non-compartmental pharmacokinetic parameters

AUCtau	The AUC calculated to the end of a dosing interval (tau) following single dose or at steady-state (amount x time x volume-1)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration or at steady-state (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration or at steady-state (time)
CL/F	The apparent total body clearance of drug from the plasma (volume x time-1)
Racc	Accumulation ratio
T1/2,eff	Effective elimination half-life

[redacted]

10.5.5.1 Data handling principles

All samples will be assayed for LEE011 concentrations by Novartis using methods that will be fully described in the CSR. Values below the assay LLOQ will be reported as 0.00 ng/mL. Missing values will be labeled accordingly.

10.5.5.2 Data analysis princplies

Analysis sets

Only PK blood samples with date and time and for which the last prior dose dates and times are adequately recorded will be included in the PK analyses. Samples taken from patients who vomited within 4 hours of dosing will be excluded from the analysis.

Basic tables, figures and listings

The individual plasma concentration versus time profiles and mean concentration versus time profile of LEE011 and analyzed metabolites (if any) will be listed, summarized and displayed graphically.

Descriptive statistics of all pharmacokinetic parameters will include arithmetic and geometric mean, median, standard deviation (SD), and Coefficient of Variation (CV), geometric CV, minimum and maximum. However, for Tmax, median values and ranges will be given. Zero concentrations will not be included in the geometric mean/CV calculation. Summaries by age group will also be provided as appropriate.

10.6 Exploratory objectives

For exploratory objectives, refer to Table 3-1.

10.6.1 Biomarkers

10.6.1.1 Outline of the data analysis

Since this clinical trial was not designed to address specific biomarkers-related hypotheses, the analysis of this data should be viewed as exploratory and hypotheses generating.

There may be circumstances when a decision is made to stop collection, or not to perform or discontinue the analysis of samples due to either practical or strategic reasons. Under such circumstances, the sample size number may be too small or the quality of the data not sufficient to perform any data analysis and the available data will be only listed.

Additional analyses that may be performed after the completion of the end-of-study CSR will be documented in separate reports. These analyses may include but are not limited to the meta-analysis of data from this study combined with data from other studies or the analysis of biomarkers generated from samples collected during the study but analyzed after the database lock and completion of the CSR. The data analysis will be described in a stand-alone analysis plan document, as appropriate.

[redacted]

10.6.1.2 Data handling principles

All measurements below their respective LLOQs or missing data will be labeled as such in the data listings. Imputation rules for measurements below the LLOQ will be described in the RAP.

Details of the data handling principles will be specified in the RAP. These will include definition of MYCN mutation (neuroblastoma) and [redacted] amplification (MRT) cutoff for gene copy numbers.

10.6.1.3 Data analysis principles

10.6.1.3.1 Analysis sets

FAS will be used for biomarker related analysis

10.6.1.3.2 Basic tables, figures and listings

Relationship between MYCN (neuroblastoma), [redacted] (MRT), other genetic alterations and anti-tumor activity at the MTD/RDE will be presented using two way tables of best overall response. Moreover, the panel of assessed genes known to be genetically altered at a frequency of at least 5% in our study population will also be listed.

Pharmacodynamic assessments of LEE011 will be evaluated by pre and post treatment bone marrow aspirate/biopsy samples analyzed for [redacted] and [redacted]. Absolute and/or relative (%) changes from baseline will be listed by subject and summarized using descriptive statistics by treatment and by visit for each biomarker. Longitudinal plots showing patient level and mean changes may also be generated.

[redacted] collected from archival tumor samples will be listed.

10.6.1.3.3 Advanced analysis methods

Additional analyses of biomarker data may be performed as needed. These will be documented in the RAP or a stand-alone analysis plan document.

10.6.2 PK-QTc relationship

Matched PK and ECG data will be used to investigate any possible relationship between LEE011 exposure (as measured by PK assessments of LEE011 plasma concentration) and QT prolongation.

To investigate the possible relationship between LEE011 concentration and change from baseline in QTcF, hereafter denoted ΔQTcF, different mixed effect models will be fitted (Table 10-3). The initial model contains only two explanatory variables, baseline QTcF and LEE011 concentration. This allows a first assessment of any possible relationship between LEE011 concentration and ΔQTcF, but without controlling for the possible confounding effects of other factors. Model 2 will be augmented with Day and Day*LEE011 concentration interaction term. If the interaction term will be non-significant it will be removed from the model before proceeding to the subsequent exploratory model in which different number of covariates of interest will be considered for inclusion (details specified in the RAP). Moreover,

[redacted]

additional models such as mixed effect model with correlation and non-linear mixed model may be used if appropriate.

[redacted]

Central tendencies

For each treatment group, mean ΔQTcF will be evaluated by time point, and the maximum mean ΔQTcF identified. A plot will be produced showing maximum mean ΔQTcF (with SD) versus dose group. This will make possible the review of the data for indication of a relationship between dose and maximum mean ΔQTcF.

A plot will be produced of mean ΔQTcF and standard error (SE) by scheduled time point representing each treatment group on the same axes. This allows the data to be reviewed for indication of a dose effect on the magnitude of mean ΔQTcF, or on the time of maximum mean ΔQTcF.

Investigation of lagged effect

The relationship between Tmax and the time of maximum ΔQTcF will be investigated graphically. For each treatment group, plots of mean LEE011 concentration by time and of mean ΔQTcF will be plotted on the same axes, using the matched ECG and PK concentration data.

10.7 Interim analysis

No formal interim analyses are planned. However, the dose-escalation design foresees that decisions based on the current data are taken before the end of the study. More precisely, after each cohort in the dose-escalation phase, the next dose will to be chosen depending on the observed data. Details of this procedure and the process for communication with investigators are provided in Section 6.2.2.

Additionally, upon completion of the first cycle of treatment for at least 10 patients within the dose expansion part, if the observed DLT rate exceeds 33%, the BLRM will be re-run to confirm that the estimated MTD/RDE still satisfies the overdose criteria of the model.

[redacted]

10.8 Sample size calculation

Dose-escalation phase

Each cohort will enroll 3 to 6 evaluable patients, including at least six patients at the MTD/RDE level and a minimum of 12 patients in total (details in Section 6.2.2). Multiple cohorts may be sequentially enrolled to the same dose level. Additional cohorts of 1 to 6 patients may be enrolled at any dose level below the estimated MTD/RDE for further elaboration of safety and pharmacokinetic parameters as required. It is expected that approximately 10 patients may be enrolled and treated within this context. In all, it is anticipated that approximately 28 patients will be treated during the escalation phase for the model to have reasonable operating characteristics relating to its MTD recommendation.

Dose expansion part

During dose expansion a sample size of approximately 18 evaluable patients per arm (including those with MRT or neuroblastoma treated at the recommended MTD/RDE during dose-escalation) will be treated to gain more information about the overall safety and tolerability of LEE011, to provide additional PK and PD data to guide the selection of dosing for future studies with LEE011, and to provide an early opportunity to identify LEE011 anti-tumor activity associated with neuroblastoma and MRT populations.

Assuming no differences in toxicity profile across the subpopulations enrolled in the expansion phase, 36 patients will result in 97% probability of detecting at least one adverse event with a true rate of 10%. This probability rises as the true adverse event rate increases.

To allow for dropouts and expansion of cohorts, it is estimated that approximately 64 patients may be treated in the entire study.

10.9 Power for analysis of key secondary variables

Not applicable

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with

[redacted]

these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a patient's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed ICF that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

Additional consent form

Studies with an optional storage of remaining biomarkers samples and additional analyses component (Section 7.2.3.3) will have a separate consent form covering those studies. This form will be adapted for each Study based on a standard template used globally for all Studies. These informed consent forms will be submitted for ethical approval together with the Study Protocol and the main informed consent form of the Study. If a patient opts not to participate in the optional assessments, this in no way affects the patient's ability to participate in the main research study.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

[redacted]

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and patient files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study CRF is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines

[redacted]

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

[redacted]

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[redacted]

14 Appendices

14.1 Appendix 1: Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

Harmonization of Efficacy Analysis of Solid Tumor Studies

Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival and Overall Survival (based on RECIST 1.1)

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Glossary

CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
DFS	Disease-free survival
eCRF	Electronic Case Report Form
FPFV	First patient first visit
MRI	Magnetic resonance imaging
LPLV	Last patient last visit
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
SOD	Sum of Diameter
TTF	Time to treatment failure
TTP	Time to progression
UNK	Unknown

[redacted]

1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy for oncology studies in solid tumors. This document is based on the RECIST criteria for tumor responses (Therasse et al 2000) and the revised RECIST 1.1 guidelines (Eisenhauer et al 2009).

The efficacy assessments described in Section 2 and the definition of best response in Section 3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 3.2 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 4 of this guideline describes data handling and programming rules. This section is to be referred to in the RAP (Reporting and Analysis Plan) to provide further details needed for programming.

2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria (Therasse et al 2000), New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16 and revised RECIST guidelines (version 1.1) (Eisenhauer et al 2009) European Journal of Cancer; 45:228-247.

2.1 Definitions

2.1.1 Disease measurability

In order to evaluate tumors throughout a study, definitions of measurability are required in order to classify lesions appropriately at baseline. In defining measurability, a distinction also needs to be made between nodal lesions (pathological lymph nodes) and non-nodal lesions.

- **Measurable disease** - the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

For patients without measurable disease see Section 3.2.8.

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.
- Cystic lesions:

[redacted]

  - Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 3.2.8.

2.2 Methods of tumor measurement - general guidelines

In this document, the term "contrast" refers to intravenous (i.v) contrast.

The following considerations are to be made when evaluating the tumor:

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.
- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to

[redacted]

MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in a UNK overall lesion response assessment. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.

- FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT are needed to determine if there is truly progression occurring at that Site (if so, the date of PD will be the date of the initial abnormal CT scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- Ultrasound: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- Endoscopy and laparoscopy: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumor markers: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit

[redacted]

differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).

- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

2.3 Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- Target lesions: All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the CRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 2.1.1.
- **Nodal target**: See Section 2.1.1.

A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

- **Non-target lesions**: All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

2.4 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 2-1) and non-target lesions (Table 2-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 2-3) as well as the presence or absence of new lesions.

[redacted]

2.4.1 Follow-up and recording of lesions

At each visit and for each lesion the actual date of the scan or procedure which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit all of the separate lesion evaluation data are examined by the investigator in order to derive the overall visit response. Therefore all such data applicable to a particular visit should be associated with the same assessment number.

2.4.1.1 Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are subject to substantial "partial volume" effects (i.e., size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

If the lesion has completely disappeared, the lesion size should be reported as 0 mm.

Measurements of non-nodal target lesions that become 5 mm or less in longest diameter are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in longest diameter irrespective of slice thickness/reconstruction interval.

In other cases where the lesion cannot be reliably measured for reasons other than its size (e.g., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

2.4.1.2 Nodal lesions

A nodal lesion less than 10 mm in size by short axis is considered normal. Lymph nodes are not expected to disappear completely, so a "non-zero size" will always persist.

Measurements of nodal target lesions that become 5 mm or less in short axis are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).Actual measurement should be given for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

[redacted]

2.4.2 Determination of target lesion response

Table 2-1 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm^2.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]

1. SOD for CR may not be zero when nodal lesions are part of target lesions
2. Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
3. Methodology change See Section 2.2.

Notes on target lesion response

Reappearance of lesions: If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point of lesion disappearance (i.e., the "0 mm" recording) be re-evaluated to make sure that the lesion was not actually present and/or not visualized for technical reasons in this previous assessment. If it is not possible to change the 0 value, then the investigator/radiologist has to decide between the following three possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 2-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- Missing measurements: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However,

[redacted]

in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.

- Nodal lesion decrease to normal size: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- Lesions split: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- Lesions coalesced: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
- Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
- Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
- Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.

[redacted]

2.4.3 Determination of non-target lesion response

Table 2-2 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline.

[1] Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician does prevail and the progression status should be confirmed later on by the review panel (or study chair).

Notes on non-target lesion response

- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless any of the lesions was not assessed (in which case response is **UNK**) or there is unequivocal progression of the non-target lesions (in which case response is **PD**).
- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

2.4.4 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded as a new lesion in the New Lesion CRF page.

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion

[redacted]

- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 2.5).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 2.2.

2.5 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 2-3.

Table 2-3 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Non-CR/Non-PD[3]	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD[1, 2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

1. This overall lesion response also applies when there are no non-target lesions identified at baseline.
2. Once confirmed PR was achieved, all these assessments are considered PR.
3. As defined in Section 2.4.

If there are no baseline scans available at all, then the overall lesion response at each assessment should be considered Unknown (UNK).

If the evaluation of any of the target or non-target lesions identified at baseline could not be made during follow-up, the overall status must be 'unknown' unless progression was seen.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

3 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 3.2.8 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

[redacted]

3.1 Best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol.

Where a study requires confirmation of response (PR or CR), changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

Longer intervals may also be appropriate. However, this must be clearly stated in the protocol. The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- For non-randomized trials where response is the primary endpoint, confirmation is needed.
- For trials intended to support accelerated approval, confirmation is needed
- For all other trials, confirmation of response may be considered optional.

The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status

[redacted]

other than a PD, e.g. PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (≥30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ≥20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

Example: In a case where confirmation of response is required the sum of lesion diameters is 200 mm at baseline and then 140 mm - 150 mm - 140 mm - 160 mm - 160 mm at the subsequent visits. Assuming that non-target lesions did not progress, the overall lesion response would be PR - SD - PR - PR - PR. The second assessment with 140 mm confirms the PR for this patient. All subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (200 mm to 160 mm) at the following assessments.

If the patient progressed but continues study treatment, further assessments are not considered for the determination of best overall response.

Note: these cases may be described as a separate finding in the CSR but not included in the overall response or disease control rates.

The best overall response for a patient is always calculated, based on the sequence of overall lesion responses. However, the overall lesion response at a given assessment may be provided from different sources:

- Investigator overall lesion response
- Central Blinded Review overall lesion response
- Novartis calculated overall lesion response (based on measurements from either Investigator or Central Review)

The primary analysis of the best overall response will be based on the sequence of investigator/central blinded review/calculated (investigator)/calculated (central) overall lesion responses.

Based on the patients' best overall response during the study, the following rates are then calculated:

Overall response rate (ORR) is the proportion of patients with a best overall response of CR or PR. This is also referred to as 'Objective response rate' in some protocols or publications.

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD.

[redacted]

Another approach is to summarize the progression rate at a certain time point after baseline. In this case, the following definition is used:

Early progression rate (EPR) is the proportion of patients with progressive disease within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of Dent and Zee (2001) and counts all patients who at the specified assessment (in this example the assessment would be at 8 weeks ± window) do not have an overall lesion response of SD, PR or CR. Patients with an unknown (UNK) assessment at that time point and no PD before, will not be counted as early progressors in the analysis but may be included in the denominator of the EPR rate, depending on the analysis population used. Similarly when examining overall response and disease control, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

3.2 Time to event variables

3.2.1 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

3.2.2 Overall survival

All patients should be followed until death or until patient has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the patient was last seen alive / last known date patient alive, the date of death and the reason of death ("Study indication" or "Other").

Overall survival (OS) is defined as the time from date of randomization/start of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last known date patient alive.

3.2.3 Time to progression

Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable "Time to progression" might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If

[redacted]

a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

3.2.4 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

Time to treatment failure (TTF) is the time from date of randomization/start of treatment to the earliest of date of progression, date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol violation' or 'Administrative problems'. The time to treatment failure for patients who did not experience treatment failure will be censored at last adequate tumor assessment.

3.2.5 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by Morgan (1988).

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates… If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in Ellis et al (2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

For summary statistics on "responders" only the following definitions are appropriate. (Specific definitions for an all-patient analysis of these endpoints are not appropriate since the status of patients throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For patients with a CR or PR (which may have to be confirmed the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

[redacted]

Duration of overall complete response (CR): For patients with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for time to progression.

Duration of stable disease (CR/PR/SD): For patients with a CR or PR (which may have to be confirmed) or SD the start and end date as well as censoring is defined the same as that for time to progression.

3.2.6 Time to response

Time to overall response (CR or PR) is the time between date of randomization/start of treatment until first documented response (CR or PR). The response may need to be confirmed depending on the type of study and its importance. Where the response needs to be confirmed then time to response is the time to the first CR or PR observed.

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 3.2.5. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)
- at last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding

Time to overall complete response (CR) is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

3.2.7 Definition of start and end dates for time to event variables

Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise - if overall lesion response is progression - the assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

[redacted]

Start dates

For all "time to event" variables, other than duration of response, the randomization/ date of treatment start will be used as the start date.

For the calculation of duration of response the following start date should be used:

- Date of first documented response is the assessment date of the first overall lesion response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively, when this status is later confirmed.

End dates

The end dates which are used to calculate 'time to event' variables are defined as follows:

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 3.2.8).

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

- Date of discontinuation is the date of the end of treatment visit.
- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.
- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

3.2.8 Handling of patients with non-measurable disease only at baseline

It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

[redacted]

It is recommended that any patients with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 3-1.

Table 3-1 Overall lesion response at each assessment: patients with non-target disease only

Non-target lesions	New Lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD[1]	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

[1] As defined in Section 2.4.

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response patients with only non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

In considering how to incorporate data from these patients into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

For ORR it is recommended that the main (ITT) analysis includes data from patients with only non-measurable disease at baseline, handling patients with a best response of CR as "responders" with respect to ORR and all other patients as "non-responders".

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with only non-measurable disease at baseline, with possible sensitivity analyses which exclude these particular patients. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from patients with only non-measurable disease.

3.2.9 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and RAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 3.2.7, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

[redacted]

Table 3-2 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after **exactly one** missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after **two or more** missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical progression was determined)	Ignored Progressed
F	New anticancer therapy given	(1) Date of last adequate assessment (2) Date of secondary anti-cancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censored Censored Event Ignored
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

1. =Definitions can be found in Section 3.2.7.
2. =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 3.2.7.
3. =The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for

[redacted]

indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment may be used as a default in this case.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 3-2 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.

In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

4 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

4.1 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

4.2 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

The end of treatment visit and its associated assessments should occur within 7 days of the last study treatment.

Patients may discontinue study treatment for any of the following reasons:

[redacted]

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

4.3 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Patients may provide study phase completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- New therapy for study indication
- Progressive disease
- Study terminated by the sponsor

4.4 Medical validation of programmed overall lesion response

As RECIST is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD), these UNK assessments may be re-evaluated by clinicians at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on

[redacted]

RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

4.5 Programming rules

The following should be used for programming of efficacy results:

4.5.1 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

4.5.2 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 3.2.7). If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

4.5.3 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

4.5.4 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

[redacted]

4.5.5 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

4.5.6 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 3-2)
- Death due to reason other than underlying cancer
- Initiation of new anti-cancer therapy

* Adequate assessment is defined in Section 3.2.7. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

[redacted]

5 References (available upon request)

Dent S, Zee (2001) application of a new multinomial phase II stopping rule using response and early progression, J Clin Oncol; 19: 785-791.

Eisenhauer E, et al (2009) New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). European Journal of Cancer, Vol.45: 228-47.

Ellis S, et al (2008) Analysis of duration of response in oncology trials. Contemp Clin Trials 2008; 29: 456-465.

FDA Guidelines: 2005 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005.

FDA Guidelines: 2007 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007.

Morgan TM (1988) Analysis of duration of response: a problem of oncology trials. Cont Clin Trials; 9: 11-18.

Therasse P, Arbuck S, Eisenhauer E, et al (2000) New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16.

[redacted]

14.2 Appendix 2: International Neuroblastoma Response Criteria (INRC)

Table 14-1 INRC definition

RESPONSE	ANATOMICAL IMAGING + MIBG (PET)
CR	● Complete resolution of non-primary measurable lesions ● MIBG non-avid (no increased FDG-PET uptake for mIBG non-avid tumors) of non-primary lesions
PR	● 30% decrease in size/sum of non-primary measurable disease (RECIST), or ● ≥ 50% reduction in MIBG score (Relative MIBG score ≥ 0.1 to ≤ to 0.5)
PD	● Any new lesion by CT/MRI or MIBG ● >20% increase in size **AND** a minimum absolute increase of 5 mm in longest dimension in existing lesions ● Relative mIBG (FDG-PET for mIBG non-avid tumors) score ≥ 1.2
SD	Neither sufficient shrinkage for MR or PR nor sufficient increase for PD

Table 14-1 describes Revised International Neuroblastoma Response Criteria written by Park J, Valteau-Couanet D, Baruchel S et al. (manuscript in preparation)

[redacted]

14.3 Appendix 3: Revised Assessment in Neuro-Oncology (RANO) Criteria

Table 14-2 RANO definition

Table 3. Criteria for Response Assessment Incorporating MRI and Clinical Factors

Response	Criteria
Complete response	Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; patients must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease.
Partial response	Requires all of the following: ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan; and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease.
Stable disease	Requires all of the following: does not qualify for complete response, partial response, or progression; stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
Progression	Defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids*; significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy* not caused by comorbid events (eg, radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (eg, seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

NOTE. All measurable and nonmeasurable lesions must be assessed using the same techniques as at baseline.
Abbreviations: MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery.
*Stable doses of corticosteroids include patients not on corticosteroids.

[redacted]

Table 14-3 Summary of RANO response criteria

Table 4. Summary of the Proposed RANO Response Criteria

Criterion	CR	PR	SD	PD
T1 gadolinium enhancing disease	None	≥ 50% ↓	< 50% ↓ but < 25% ↑	≥ 25% ↑*
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑*
New lesion	None	None	None	Present*
Corticosteroids	None	Stable or ↓	Stable or ↓	NA†
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓*
Requirement for response	All	All	All	Any*

Abbreviations: RANO, Response Assessment in Neuro-Oncology; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; FLAIR, fluid-attenuated inversion recovery; NA, not applicable.
*Progression occurs when this criterion is present.
†Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

Table 14-2 and Table 14-3 is described in Updated Response Assessment Criteria for High Grade Glioma: Response Assessment in Neuro-Oncology Working Group. Journal of Clinical Oncology, Vol 11, No 8 (August), 1993: pp 1466-1477.

14.4 Appendix 4: Karnofsky Performance Status Scale (for patients greater than 16 years old)

Table 14-4 Karnofsy Performance Status Scale

Able to carry on normal activity and work; no special care needed	100%	Normal; no complaints
	90%	Able to carry on normal activity; minor signs or symptoms of disease
	80%	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	70%	Cares for self; unable to carry on normal activity or work
	60%	Requires occasional assistance; able to care for most personal needs
	50%	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40%	Disabled; requires special care and assistance
	30%	Severely disabled; hospitalization is indicated though death not imminent
	20%	Very sick; hospitalization necessary; active supportive treatment necessary
	10%	Moribund; fatal processes progressing rapidly
	0	Dead

[redacted]

14.5 Appendix 5: Lansky Score (for patients less than or equal to 16 years old)

Table 14-5 Lansky score

100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both greater restriction of play and less time spent in play activity
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed but lies around much of the day; no active play but able to participate in all quiet play and activities
40	Mainly in bed; participates in quiet activities
30	Bed-bound; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities
10	No play; does not get out of bed
0	Unresponsive

14.6 Appendix 6: Medication and herbals to be excluded or to be used with caution

Any patient who requires a prohibited medication should not be enrolled on a trial for LEE011 until further information becomes available.

Note: This is not a comprehensive list of cytochrome P450 isoenzymes and QT prolongation medications. This is only meant to be used as a guide. Please contact the medical monitor with any questions.

CYP3A4/5

In order to avoid clinically significant drug-drug interactions, the co-administration of known CYP3A4/5 substrates with narrow therapeutic windows will be prohibited (Table 14-6). Additionally, considering LEE011 is a substrate of CYP3A4, strong inducers and inhibitors of CYP3A4 will also be contraindicated (Table 14-6). Medications that are moderate or weak inhibitors or inducers of CYP3A4/5, are permitted in this study, however they should be used with caution (Table 14-7). In addition, sensitive substrates of CYP3A4/5, that do not have a narrow therapeutic index are permitted, but should be used with caution (Table 14-7).

[redacted]

Table 14-6 List of contraindicated CYP3A substrates, inducers or inhibitors

Category	Drug Name
Strong CYP3A Inhibitors – AUC substrate increased by ≥ 5 fold	Boceprevir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir, Clarithromycin, telithromycin, troleandomycin, itraconazole, ketoconazole, voriconazole, posaconazole, mibefradil, nefazodone, conivaptan, grapefruit juice
Strong CYP3A Inducers – AUC decreased by ≥ 80%	carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, Avasimibe,[2]St. John's wort
[1] CYP3A substrates with narrow therapeutic index (NTI)	alfentanil, fentanyl, pimozide, astemizole, terfenadine, cyclosporine, sirolimus, tacrolimus, dihydroergotamine, ergotamine, quinidine, cisapride

[1] Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).
[2] Herbal product
This list of CYP substrates was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table (http://medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.aspx; accessed April 4th, 2012),from the FDA's "Drug Interaction Studies —Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations, DRAFT GUIDANCE, February 2012 (For further information, please see the FDA's website: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf (accessed April 04, 2012)"

Table 14-7 List[1] of medications which are CYP3A substrates, inducers or inhibitors to be used with caution

Category	Drug Name
Sensitive CYP3A substrates[2]	brotizolam, midazolam, triazolam, ebastine, felodipine, nisoldipine, quetiapine, lovastatin, simvastatin, alpha-dihydroergocryptine, budesonide, buspirone, darifenacin, dasatinib, dronedarone, eletriptan, eplerenone, fluticasone, lurasidone, perospirone, sildenafil, ticagrelor, vardenafil
Moderate CYP3A inhibitors – AUC substrate increased by 2 to 5 fold	Amprenavir, aprepitant, atazanavir, clozapine, cimetidine, ciprofloxacin, crizotinib, darunavir, diltiazem, domperidone, elvitegravir, erythromycin, fluconazole, fosamprenavir, imatinib, lapatinib, losartan, mianserin, mifepristone, naftidrofuryl, nicardipine, ondansetron, oxatomide, pazopanib, pirenzepine, raloxifene, sorafenib, ticlopidine, schisandra sphenanthera, tipranavir, tofisopam, verapamil
Moderate CYP3A Inducers - AUC decreased by 50-80%	Bosentan, efavirenz, etravirine, modafinil, nafcillin, ritonavir, talviraline, tipranavir

[1] Any drug mentioned in the above list should be contraindicated if they are excluded based on any other exclusion criteria as specified in Section 5.3 of the Study Protocol
[2] Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor.
[3] Herbal product
This list of CYP substrates was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table (http://medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.aspx; accessed April 4th, 2012),from the FDA's "Drug Interaction Studies —Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations, DRAFT GUIDANCE, February 2012 (For further information, please see the FDA's website: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf (accessed April 04, 2012))"

CYP1A2

The co-administration of known CYP1A2 substrates with a narrow therapeutic index and agents that are strong inhibitors of CYP1A2 are to be used with caution (Table 14-8).

[redacted]

Table 14-8 List[1] of medications which are CYP1A2 substrates with narrow therapeutic index (NTI) or strong inhibitors of CYP1A2

Category	Drug Name
Strong CYP1A2 Inhibitors – AUC substrate increased by ≥ 5 fold	enoxacin, fluvoxamine
[2]CYP1A2 substrates with narrow therapeutic index (NTI)	alosetron, clozapine, duloxetine, clinafloxacin, melatonin, olanzapine, ramelteon, rofecoxib, tacrine, theophylline, tizanidine, zafirlukast

[1] Any drug mentioned in the above list should be contraindicated if they are excluded based on any other exclusion criteria as specified in Section 5.3 of the Study Protocol
[2] Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor.
This list of CYP substrates was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table (http://medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.aspx; accessed April 4th, 2012),from the FDA's "Drug Interaction Studies —Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations, DRAFT GUIDANCE, February 2012 (For further information, please see the FDA's website: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf (accessed April 04, 2012))",
and from the University of Washington's Drug Interaction Database

BSEP transporter

In order to avoid clinically significant drug-drug interactions, the co-administration of known BSEP inhibitors causing further BSEP inhibition are to be used with caution (Table 14-9).

Table 14-9 BSEP transporter: List of medications causing inhibition to be used with caution

Drug Name	Drug Class
Bosentan	Antihypertensive
Cyclosporin A	Immunosuppressant
Fusidate	Antibiotic
Glibenclamide	Sulfonylurea
Lovastatin	Antihyperlipidemic
Nefazodone	Antidepressant
Rifampicin	Antitubercular
Ritonavir	Antiretroviral
Sulindac	Nonsteroidal anti-inflammatory
Troglitazone (TGZ-sulfate)	Anti-diabetic

QT prolongation

Due to the concern that LEE011 will cause QT prolongation, caution should be exercised with all medications that are known to produce this effect. Those known to have a strong signal will be prohibited (Table 14-10) and others are to be used with caution (Table 14-11).

[redacted]

Table 14-10 QT prolongation: List of excluded medications

Drug Name	Drug Class
Amitriptyline, Desipramine, Imipramine	Antidepressants
Chloroquine	Antimalarials
Chlorpromazine, Mesoridazine, Risperidone	Antipsychotics
Itraconazole, Ketoconazole	Antifungals
Tacrolimus, Arsenic trioxide, Domperidone	Miscellaneous drugs

Table 14-11 QT prolongation: List of medications to be used with caution

Drug Name	Drug Class
Dolasetron, Ondansetron, Tropisetron	Anti-emetics
Doxepin, Maprotiline, Venlafaxine,	Antidepressants
Gatifloxacin, Moxifloxacin, Sparfloxacin	Quinolone antibiotics
Halofantrine	Antimalarials
Pentamidine, Droperidol, Methadone, Bepridil	Miscellaneous drugs
Thioridazine, Ziprasidone,	Antipsychotics

14.7 Appendix 7: Prior calibration and operating characteristics of the Bayesian logistic regression model (BLRM)

Statistical model and dose recommendation

An adaptive BLRM with 2 parameters, guided by the EWOC principle, will be used to make dose recommendations and estimate the MTD/ RDE during the study. The use of Bayesian response adaptive models for Phase I studies has been advocated by the EMEA guideline on small populations, 2006 and by Rogatko et al (2007) and is one of the key elements of the FDA's Critical Path Initiative.

The adaptive BLRM will be fitted on the dose-limiting data (i.e. absence or presence of DLT) accumulated in cycle 1 throughout the dose escalation and the dose expansion parts of the study, for modeling the dose-DLT relationship of LEE011.

The DLT relationship in the escalation and escalation parts of the study will be described by the following Bayesian logistic regression model:

$$\text{logit}(\pi_{(d)}) = \log(\alpha) + \beta \log(d/d^*), \qquad \alpha>0,\ \beta>0$$

where $\text{logit}(\pi_{(d)}) = \ln(\pi_{(d)}/(1-\pi_{(d)}))$, and $\pi_{(d)}$ is the probability of a DLT at dose d. Doses are rescaled as d/d* with reference dose of $d^* = 580$ mg/m^2. As a consequence α is equal to the odds of the probability of toxicity at d*. Note that for a dose equal to zero, the probability of toxicity is zero.

If a different dosing schedule will be considered, a Bayesian Meta-analytic approach will be used to take into account historical data collected for the initially planned schedule in the actual study, in order to derive an informative prior estimation of the dose-toxicity relationship for the new dosing regimen.

[redacted]

Prior specifications

The Bayesian approach requires the specification of prior distributions for the model parameters. All information currently available about the dose-DLT relationship of LEE011 was summarized in a prior distribution. [redacted]

- [redacted]
- Estimation of the MTD/RDE in the dose-escalation part of the current study will take into account patients in the dose-determining set and will be based upon the estimation of the probability of DLT in the Cycle 1, [redacted] by 28 days.
- [redacted]
- For the pediatric population subject to inclusion/exclusion criteria studied in the current trial, it is expected that the probability of DLT within cycle 1 at any given LEE011 doses administered in mg/m^2 is similar to the probability of DLT within cycle 1 at the corresponding flat LEE011 dose administered in the adult population [redacted].

- [redacted]
  - [redacted]
  - [redacted]
- [redacted]
  - [redacted]
  - [redacted]
- [redacted]

[redacted]

[redacted]

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- For the remaining doses, the prior [redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

Hypothetical dose escalation scenarios

In order to show how the Bayesian model reacts, different hypothetical dose escalation scenarios were investigated. The design should make reasonable dose-recommendations during the clinical trial based on the observed DLTs. During the study, the decision to dose escalate after completion of a given cohort and the actual dose chosen for the subsequent cohort will depend on the recommendation of the BLRM per EWOC principle and medical review of available clinical and laboratory data.

Note that the next dose level is selected in concordance with the provisional dose levels specified in Section 6.2.1 of the protocol, to mimic possible on-study escalation steps. For example, in scenario 1 (0/3 at 280 mg/m^2), the next dose level is below the maximal increase allowed by the model and below the 100% increase limit. However, since this is one of the provisional dose levels suggested for the next cohort, it has been selected.

Additionally, for the scenarios in which a high toxicity rate is observed at the starting dose level (2/3 DLTs, scenario 3), a dose of 85 mg/m^2 has been added in order to show cases in which future re-escalations of the compound may be recommended.

Some scenarios to illustrate the dose escalation up to the third dose cohort are listed in Table 14-15. Some scenarios illustrate the ability for the model to handle cohorts of different size.

[redacted]

Table 14-15 Scenarios

scenario	LEE011 dose	Npat	Ntox	Next dose level (NDL)	P(target) NDL	P(over) NDL	Median DLT rate
1	280 mg/m^2	3	0	420 mg/m^2	31.5%	7.5%	13.7%
2	280 mg/m^2	3	1	280 mg/m^2	43.3%	16.9%	19.5%
3	280 mg/m^2	3	2	85 mg/m^2	35.7%	25%	20.3%
4	280 mg/m^2 420 mg/m^2	3 3	0 0	630 mg/m^2	31.8%	10.2%	14.1%
5	280 mg/m^2 420 mg/m^2	3 3	0 1	420 mg/m^2	45.9%	10.8%	18.3%
6	280 mg/m^2 420 mg/m^2	3 3	0 2	280 mg/m^2	48%	15.4%	20.1%
7	280 mg/m^2 280 mg/m^2	3 3	1 0	420 mg/m^2	46%	13%	18.9%
8	280 mg/m^2 85 mg/m^2	3 3	2 0	210 mg/m^2	45.6%	22.7%	22%
9	280 mg/m^2 420 mg/m^2	3 6	0 2	420 mg/m^2	55.5%	13.9%	20.9%
10	280 mg/m^2 420 mg/m^2	3 6	0 3	280 mg/m^2	53.7%	15.2%	21.4%
11	280 mg/m^2 420 mg/m^2 630 mg/m^2	3 3 3	0 0 0	850 mg/m^2	25.3%	7.2%	11.9%
12	280 mg/m^2 420 mg/m^2 630 mg/m^2	3 3 3	0 0 1	630 mg/m^2	43.9%	14.2%	18.7%
13	280 mg/m^2 420 mg/m^2 630 mg/m^2	3 3 3	0 0 2	420 mg/m^2	48.7%	10.1%	18.6%
14	280 mg/m^2 420 mg/m^2 630 mg/m^2	3 3 6	0 0 2	630 mg/m^2	52.1%	16.4%	21.2%
15	280 mg/m^2 420 mg/m^2 630 mg/m^2	3 3 6	0 0 3	420 mg/m^2	53.2%	9%	19.2%
16	280 mg/m^2 420 mg/m^2 630 mg/m^2 420 mg/m^2	3 3 3 6	0 0 2 0	* 420 mg/m^2	31.3%	1.6%	13.2%

* the next dose level is selected in concordance with the provisional dose levels specified in Section 6.2.1 but in this case intermediate doses between 630 mg/m^2 420 mg/m^2 would be more appropriate and are allowed as per EWOC.

Within Table 14-14, it can be seen that the model leads to decisions that are in agreement with clinical sense: progressive increase of the LEE011 doses if no DLT is observed, enrolling of a new cohort at the same dose level when 1/3 or 2/6 DLT's are reported, and decrease when more than 1 or 2 DLTs are reported in cohorts of 3 or 6 patients respectively.

[redacted]